REVIEW ARTICLE

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Safety of Antihistamines in Children

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Abstract

The histamine H_1 receptor antagonists (antihistamines) are an important class of medications used for the relief of common symptoms associated with hyperhistaminic conditions occurring in children and adults. This group of drugs may

be subdivided into 3 classes, or generations, based upon their propensity to induce sedation and cardiotoxicity.

The first generation (classical) antihistamines are highly effective in treating hyperhistaminic conditions. However, they frequently induce sedation and may adversely affect a child's learning ability. First generation antihistamine–induced sedation has been described to occur in more than 50% of patients receiving therapeutic dosages. Serious adverse events are unusual following overdoses of first generation antihistamines although life-threatening adverse events have been described.

When the so-called 'second generation' antihistamines terfenadine and astemizole were introduced they were widely embraced and quickly used by clinicians of all specialities, including paediatricians, as nonsedating alternatives to the first generation compounds. These new agents were found to be equally or more effective than first generation antihistamines in relieving symptoms associated with hyperhistaminic conditions without the soporific effects of the first generation agents. Unfortunately, after approximately 10 years of widespread clinical use, disturbing reports of potentially life-threatening dysrhythmias, specifically torsades de pointes, were described. Both terfenadine and astemizole have been shown *in vitro* to inhibit several ion channels, and in particular the delayed outward rectifier potassium channel in the myocardium, predisposing the heart to dysrhythmias.

The potential life-threatening cardiotoxicities of the second generation antihistamines led to the search for noncardiotoxic and nonsedating agents. Loratadine, fexofenadine, mizolastine, ebastine, azelastine and cetirizine are the first of the new third generation antihistamines. These drugs have been shown to be efficacious with few adverse events including no clinically relevant cytochrome P450 mediated metabolic–based drug-drug interactions or QT interval prolongation/cardiac dysrhythmias.

Appropriate treatment of an antihistamine overdose depends upon which class of compound has been ingested. There is no specific antidote for antihistamine overdose and treatment is supportive particularly for ingestions of first generation compounds. Ingestion of excessive doses of terfenadine or astemizole requires immediate medical attention. Children who accidentally ingest excessive doses of a third generation compound may usually be adequately managed at home. However, patients ingesting large amounts (approximately >3 to 4 times the normal therapeutic daily dose) should receive medical attention. These patients should be monitored for 2 to 3 hours after the ingestion and patients ingesting cetirizine should be advised about the potential for sedation.

The availability of newer generation antihistamine compounds has clearly added to the clinical effectiveness and patient tolerance of a widely prescribed class of drugs. These advances have also been accompanied by improved safety profiles, particularly in the case of third generation antihistamine overdose.

Many drugs are classified based upon various drug/class-specific properties including receptor specificity, pharmacokinetic properties, safety profiles, etc. With the histamine H_1 receptor antagonists (antihistamines), it has become common to classify these agents into 'generations', based upon their propensity to induce sedation and cardiac toxicity. Although this approach to classification has been accepted by many[1] some authors questions this approach, though offering no alternatives.[2] For the

Table I. Histamine H_1 receptor antagonists (antihistamines) prescribed to children categorised by generation and chemical class

First generation[a] (classical/sedating)
Alkylamines
Brompheniramine maleate[b]
Chlorpheniramine maleate[b]
Dexbrompheniramine
Dexchlorpheniramine
Dimethindene
Phiramine
Pyrrobutamine
Triprolidine
Ethanolamines
Bromodiphenhydramine
Carbinoxamine
Clemastine fumarate[b]
Dimenhydrinate
Diphenhydramine
Diphenylpyraline
Doxylamine
Phenyltoloxamine
Ethylenediamine
Antazoline
Pyrilamine maleate[b]
Tripelennamine hydrochloride
Phenothiazines
Methdilazine
Promethazine
Trimeprazine
Piperidines
Azatadine
Buclizine
Cyclizine
Cyproheptadine hydrochloride
Hydroxyzine
Meclizine[b]
Second generation (nonsedating/cardiotoxic)
Astemizole[c]
Terfenadine[c]
Third generation (nonsedating/ noncardiotoxic)
Azelastine
Cetirizine
Ebastine
Fexofenadine
Loratadine
Mizolastine

a Subdivided by chemical class.
b Available over the counter.
c Removed from US market.

purposes of this paper, first generation (classical) agents comprise drugs that effectively antagonise H_1 receptors but are associated with sedation, which can be profound. Second generation agents are those agents that antagonise H_1 receptors without associated drug-induced sedation but clinically are associated with important cardiotoxicities. Lastly, third generation compounds are those antihistamines, which effectively antagonise H_1 receptors producing little to no sedation and no clinically important adverse effects, including associated cardiotoxicities with their routine clinical administration.

Both second and third generation antihistamines possess much less affinity for nonhistamine receptors as compared with first generation agents. This receptor selectivity of second and third generation agents is reflected in the marked reduction in adverse effects associated with their use. Nevertheless, the second generation agent astemizole has been associated with stimulation of appetite, which may result in bodyweight gain.[3-5] Most second and third generation antihistamines have been occasionally linked to the occurrence of other adverse events including hepatitis, alopecia and skin rashes although causality with the use of these medications has not been proven.[6] In contrast, first generation antihistamines bind to additional nonhistamine receptors [e.g. serotonin (5-hydroxytryptamine) and cholinergic receptors], and this is most likely the mechanism behind many of the bothersome adverse events associated with the use of these agents.[7]

The failure to adequately treat symptoms associated with many allergic disorders is a common source of discomfort that can adversely influence a child's quality of life and school performance.[8,9] For decades first generation antihistamines have been prescribed to children for the treatment of symptoms associated with many common disorders including allergic rhinitis, conjunctivitis, allergic skin disorders (i.e. atopic dermatitis, urticaria and dermagraphism) and for anaphylactic/ anaphylactoid reactions (table I). Although the first generation antihistamines have been extremely useful in the prevention and treatment of many common conditions associated with histamine release

and excess, the very common occurrence of minor but sometimes undesirable adverse events limit their overall therapeutic potential. Unfortunately, sedation, one of the most common adverse effects associated with their use, may negatively impact upon a child's social and academic growth.[10-12]

1. First Generation Histamine H_1 Receptor Antagonists (Antihistamines)

1.1 Overview

The first generation antihistamines, which include several different chemical classes of compounds (table I), competitively antagonise histamine at the H_1 receptor.[7,13] Adverse events associated with their administration include sedation, dizziness, headache, insomnia, nervousness, nausea, vomiting, constipation, diarrhoea, dry mouth, urinary retention, impotence, appetite stimulation and bodyweight gain.[6,13] The first generation antihistamines have historically been categorised by their chemical structure with similar antihistamines within a chemical class tending to share the same propensity to induce a similar type and frequency of adverse events. For example, the ethanolamine class of antihistamines (i.e. diphenhydramine and clemastine), are considered highly sedating with few concurrent gastrointestinal adverse effects.[7,13] In contrast, the alkylamines (e.g. chlorpheniramine) do not appear to be associated with substantial drowsiness in many patients.[7,13] Of course, each particular antihistamine within a chemical class has its own particular adverse effect profile reflecting an inherent intraclass variability in biological activity. Levocabastine is a relatively new antihistamine for topical application marketed in Europe and other countries but not in the US. The oral and intravenous formulations of levocabastine are not clinically useful because of the high incidence of associated sedation with little added benefit over older first generation antihistamines.[14] When administered as an ophthalmological or intranasal topical formulation, patients experience apparent local clinical benefit with little to no systemic clinical or sedative effects due to the limited systemic availability.[14]

1.2 Sedation Associated with First Generation Antihistamines

Although particular first generation antihistamines may be associated with less sedation than others (table II), sedation associated with this group of antihistamines is so common that these antihistamines have been termed by the US Food and Drug Administration (FDA) as 'sedating antihistamines'.[15] First generation antihistamines have consistently demonstrated soporific and cognitive impairments[16] and are commonly used as a verum (positive control) in clinical trials assessing sedation. The term sedation is commonly used to describe the patient's subjective assessment of their level of alertness, decreased concentration and somnolence. More correctly, the term sedation is a measurable attribute that encompasses higher cognitive function impairment, including attention, memory,

Table II. Relative degree of histamine H_1 receptor antagonist (antihistamine)–induced sedation for selected agents

Antihistamine compound by generation	Relative degree of sedation
First generation (classical) agents	
Brompheniramine	++
Chlorpheniramine	++
Clemastine	++
Cyproheptadine	++
Dexbrompheniramine	++
Diphenhydramine	+++
Hydroxyzide	+++
Ketotifen	+
Promethazine	+++
Pyrilamine	++
Triprolidine	++
Second generation agents	
Astemizole	+/–
Terfenadine	+/–
Third generation agents	
Azelastine	+/–
Cetirizine	+
Ebastine	+/–
Fexofenadine	+/–
Levocarbastine	+/–
Loratadine	+/–

+ = mildly sedating; ++ = moderately sedating; +++ = highly sedating; +/– = equivalent to placebo.

coordination and psychomotor performance.[16] Many of the first generation antihistamines are available to the consumer over the counter as sleeping aids underscoring their soporific effects. Approximately 25 to 55%[17-20] of patients administered therapeutic dosages of first generation antihistamines appear to be affected with sedation thereby severely limiting their clinical usefulness.

1.3 Determination of Sedation

Several objective and subjective instruments have been used to quantify the sedative effects of drugs. Simulated or actual car driving assesses the effects of a drug on motor performance and its soporific effects. Nevertheless, these tools may be impracticable to perform in certain patient populations such as children or nondriving adults. The critical flicker fusion task is a noninvasive test that measures the cognitive capacity of the patient and appears to be an extremely sensitive tool. One of the more commonly used instruments is the multiple sleep latency test, which determines the length of time it takes to induce any stages of sleep on the electroencephalogram. Decreased latency time to sleep indicates soporific effects. Other objective measures include P300, which measures cognitive function, and choice reaction time (CRT), which measures reaction time, comprised of recognition and motor reaction time. Subjective instruments such as the visual analogue scale (VAS), where patients assess their sleepiness may also be helpful. Nevertheless, these subjective findings may not parallel objective findings using more objective critical measures. However, most of the objective and subjective research instruments listed here have been associated with important limitations, which include the fact that few are validated and the results they provide may not be reproducible.[16] When assessing drug induced sedation, a battery of tests which measures different aspects of cognitive and psychomotor performance should be preformed to determine the overall sedative effects of the particular drug.

1.4 Receptor Basis for Antihistamine-Induced Sedation

Traditionally, sedation associated with first generation antihistamines was believed to occur when these antihistamines crossed the blood brain barrier binding to centrally located acetylcholine receptors producing sedation and other anticholinergic effects.[21] The proposed mechanism for antihistamine-induced sedation has evolved slowly as our knowledge of histamine and its receptors has increased in the last few years. Levels of histamine that is released within the CNS increase during waking and wane during time of sleep suggesting a circadian rhythm[22,23] and a role for histamine in the sleep-wake cycle. This belief of histamine's role in the sleep-wake cycle is further supported by the observation that inhibition of histidine decarboxylase in rats impairs their waking.[24] Antagonism of postsynaptic H_1 receptors in the tuberomammillary nucleus, which is known to regulate the sleep-wake cycle in mammals,[23,25] by the administration of first generation antihistamines inhibits histamine-induced depolarisation. This does not occur after administration of H_2 or H_3 antagonists[26] (i.e. cimetidine and thioperamide, respectively) suggesting that histamine induced depolarisation is solely mediated by presynaptic H_1 receptors. Therefore, first generation antihistamines may induce sedation by their direct antagonism of centrally located H_1 receptors.

With the recent discovery of the H_3 receptor,[27] the role of histamine has expanded to include that of a neurotransmitter[25] with possible mediation of many diverse physiological functions. Although not fully elucidated, histamine and H_3 receptors may act as a negative feedback pathway for several different cascades and be associated with migraine headaches, myocardial regularity, gastrointestinal tract secretion, inflammation cascade, and various functions within the CNS including modulation of the sleep-wake cycle.[25] This newly discovered receptor is found peripherally and centrally within the cortex of the brain. Activation of presynaptic H_3 receptors inhibits the synthesis and release of histamine and is also believed to inhibit acetylcholine,

serotonin, noradrenaline (norepinephrine) and dopamine release.[28,29] Although its overall function has not been fully elucidated, this receptor has been demonstrated to be involved in histamine-induced sedation.[30,31] Activation of H_3 receptors in the dura mater of guinea-pigs by a selective H_3 agonist decreases motor activity and increases total sleep time with electroencephalogram tracings consistent with physiological sleep.[32] Conversely, the sedative effects of an H_3 receptor agonist were ameliorated with the administration of thioperamine, an H_3 receptor antagonist,[32] confirming the role of H_3 receptors in the sleep-wake cycle.[33] These observations suggest that antagonism of central H_1 receptors by first generation antihistamines may permit circulating histamine to interact with other receptors, such as central H_3 receptors culminating in sedation. Although this hypothesis is very appealing, further research is needed to fully evaluate the role of the H_3 receptor in sedation.

1.5 Learning Impairment Associated with First Generation Antihistamines

Adverse effects of the first generation antihistamines, particularly drowsiness, appear to be associated with the peak concentration of the agent.[34,35] Although inconsistent, the patient may develop tolerance to sleepiness induced by first generation antihistamines.[36] Unfortunately, many children do not continue therapy long enough to develop tolerance because the drug is either discontinued because of excessive sedation or the duration of therapy is short. In children with hyperhistaminic conditions, both inadequacy in treatment[37] and treatment consisting of first generation antihistamines have been demonstrated to lead to diminished quality of life, impaired learning[8-10,12] and decreased learning performance.[10,11,38,39] Untreated symptomatic atopic adults have been described to experience decreased verbal learning, slower decision making and slower psychomotor speed when compared with healthy adults.[40] Much of this difference disappears when the atopic adults are no longer symptomatic (i.e. during winter months). Using a computer simulation, Vuurman and colleagues[8] described the effect of allergic rhinitis and its treatment on children's learning ability in 3 important areas, including factual, conceptual, and application of knowledge. Children with a history of seasonal allergic rhinitis receiving diphenhydramine scored significantly lower ($p < 0.05$) in all 3 areas when compared with healthy children. Although not significantly different there was a trend for the patients treated with diphenhydramine to have consistently lower scores than those receiving placebo. This possible deleterious effect of first generation antihistamines on children's learning was later confirmed[41] underscoring the desire to avoid the use of these agents in children.

1.6 Toxic Ingestion of First Generation Antihistamines

The widespread use of first generation antihistamines in paediatrics has been accompanied by frequent intoxication.[42] Typically, children ingesting large quantities of first generation antihistamines experience marked sedation, lethargy and anticholinergic-like symptoms including dry mouth, tachycardia, and hyperactivity with potential progression to acute psychosis[43,44] (table III). Koppel et al.[45] in a retrospective study described 136 patients who ingested diphenhydramine (dose range 0.3 to > 5000mg; 20% of patients ingested an unknown amount). Two-thirds of the patients were aged between 14 and 30 years old. Of these 136 patients, 29 patients were identified when they were hospitalised (group I) and the remaining 107 patients (group II) were included in the study after their local poison control centre had been contacted. The most frequent symptom reported in both groups of patients (hospitalised and poison control contact) was somnolence; occurring in approximately 34 and 36% of patients, respectively. Approximately 23 and 27% of hospitalised and poison control centre managed patients, respectively, experienced psychosis. Coma was described more frequently in patients requiring hospitalisation than patients managed by a poison control centre, 14 and 6%, respectively. Hallucinations and mydriasis were experienced by approximately 7 to 8% of

all patients. Tachycardia and respiratory insufficiency occurred in approximately 3% of hospitalised patients. Seizures and diplopia, which were unwitnessed in the nonhospitalised patients, were described to occur in 3 and 2% of all patients. Overall, approximately 16 and 30% of patients hospitalised and those managed by a poison control centre, respectively, experienced no symptoms associated with diphenhydramine ingestion.

Seizures, which can occur following intoxication with a first generation antihistamine, occur more frequently in children than adults. Depending upon the amount ingested, seizures and life-threatening symptomatology such as ventricular dysrhythmias,[46-49] cardiopulmonary arrest[43,48,49] and refractory seizures[44,46,47,49] as well as death[44,48,49] have been described in intoxicated paediatric patients. The potential for the development of seizures and potentially life threatening reactions underscores the need for prompt and effective treatment of severely intoxicated patients. Unfortunately, no specific therapy other than aggressive supportive measures is effective in the treatment of these patients.

Table III. Typical signs and symptoms associated with histamine H_1 receptor antagonist (antihistamine) intoxication

First generation (classical) [e.g. diphenhydramine, hydroxyzine]
Dry mouth
Drowsiness, lethargy
Nausea/vomiting
Flushing
Fever
Hyperactivity/irritability
Tachycardia
Diarrhoea
Mydriasis
Slurred speech
Ataxia, stupor
Psychosis
Seizures
Coma
Second generation (e.g. terfenadine, astemizole)
Nausea/vomiting
Headaches
Dry mouth
Anticholinergic effects
Cardiac dysrhythmias
Third generation (e.g. loratadine, fexofenadine, cetirizine)
Sedation
Extrapyramidal reactions
Palpitations
Tachycardia
Headaches

2. Second Generation Antihistamines

2.1 Overview

The relatively common occurrence of antihistamine-induced adverse effects at therapeutic dosages limited the use of first generation antihistamines and stimulated the search for newer analogues with improved safety profiles. The second generation antihistamines (table I) were the first of this new class of agents that afforded an apparently improved safety profile. In particular they were far less sedating than the first generation agents. Terfenadine and astemizole were the first of the second generation antihistamines marketed. Both of these agents have been shown to posses equal or possibly superior antihistaminic activity to first generation antihistamines in children and adults experiencing hyperhistaminic conditions.[3-5] Moreover, the absence of clinically important sedation with these agents represented a major therapeutic advance in antihistamine therapy. Approximately 6 years after receiving FDA approval in 1991, terfenadine became the ninth most prescribed medication in the US.[50] Both of these second generation antihistamines were FDA labelled for use in older children and adults although paediatricians quickly utilised available liquid formulations of both drugs for the treatment of their younger patients.[51]

2.2 Pharmacokinetics of Second Generation Antihistamines

Paediatric pharmacokinetic studies with terfenadine and astemizole have been sparse and the available data are summarised in table IV. Once absorbed both terfenadine and astemizole undergo ex-

Table IV. Disposition characteristics of second and third generation histamine H_1 receptor antagonists (antihistamines) in children and adults

Antihistamine	Half-life		Volume of distribution (L/kg)	Plasma protein binding (%)	Route of elimination	Active metabolite
	Parent (h)	Metabolite (h)				
Astemizole [3,52-54]						
Children	NR	11.2 (days)	ND	ND	Metabolised by CYP3A4 and excreted by the kidneys and via bile	Yes: desmethylastemizole
Adults	20	11.8 (days)	250	97		
Azelastine[55]						
Adults	22-36	42-54	14.5	78-88	Metabolised by CYP3A4 and other alternative pathways; excreted by the kidneys and faeces possibly via bile	Yes: desmethylazelastine
Cetirizine[56-60]						
Infants	3.1	None	0.7	ND	Not metabolised. Excreted unchanged by the kidneys	No
Toddlers	4.9	None	0.58	ND		
Children	7.1	None	0.44	ND		
Adults	8.6	None	0.63	99		
Ebastine[a] [61-63]						
Children	Minutes	14	2.1-2.4	ND	Metabolised by CYP3A4 and 2D6 and excreted via the urine	Yes: carebastine
Adults	Minutes	10-16	1.5-2	98		
Fexofenadine[54,64,65]						
Children	17.6	None	ND	ND	Not metabolised. Excreted unchanged by the kidneys	No
Adults	14.4	ND	5.8	60-70		
Loratadine[54,66]						
Children and Adults	8.4	28	119	97-99	Metabolised by CYP3A4 and 2D6 and excreted by the kidneys and via bile	Yes: descarboethoxyloratadine
Mizolastine[14]						
Adults	8-10	None	1.0-1.4	98	Metabolised by CYP3A4 and 2C6 and excreted by the faeces	None
Terfenadine[4,5,54]						
Children	NR	17.6	NR	ND	Metabolised by CYP3A4 and excreted by the kidneys and via bile	Yes: fexofenadine (terfenadine carboxylate)
Adults	NR	14.4	ND	97		

a Data reflects the metabolite, carebastine.

CYP = cytochrome P450; **ND** = no data (located following a search of the English language literature); **NR** = not reported.

tensive first pass metabolism via cytochrome P450 (CYP) 3A4. Terfenadine, which is nearly inactive, is completely and rapidly metabolised (approximately 99.5%) to its active metabolite, terfenadine carboxylic acid (also known as fexofenadine).[67] The half-life of terfenadine, the parent compound,

is ill defined as most studies report the half-life of its metabolite, which is approximately 14 to 18 hours. Similarly, astemizole undergoes metabolism via CYP3A4 to 3 major metabolites, desmethyl astemizole (DMA), norastemizole and 6-hydroxydesmethylastemizole (6-HDMA). DMA, the major metabolite of astemizole,[68] and norastemizole[1,69] appears to possess antihistaminic properties approaching those of the parent compound whereas 6-HDMA possesses substantially less activity.[70] The half-life of astemizole and its metabolites in children have been reported to be approximately 11.2 days.[52] Both astemizole and terfenadine appear to be extensively distributed in the body though no reports have described the apparent volume of distribution for terfenadine in either children or adults. In contrast the apparent volume of distribution for astemizole is approximately 250 L/kg[3] in adults reflecting the drugs high degree of tissue binding.

2.3 Adverse Events Associated with Second Generation Antihistamine Administration

In clinical trials both terfenadine and astemizole were reported to be well tolerated. Initially, the type and severity of adverse effects seen with these two agents were described as being no different in type and incidence to those seen with placebo.[20] Between 2.8 and 12% of patients evaluated in various studies complained of sedation while receiving either terfenadine or placebo.[51,71-73] Similarly 14.7 and 13.3% of children and adults treated with astemizole or placebo, respectively, complained of CNS depression.[20] As an example of the broad-based patient acceptance of these second generation antihistamines, only 1% of 744 adult patients receiving these medications compared with 5 to 6% of patients receiving first generation antihistamines discontinued therapy because of unacceptable sedation.[3] Sedation associated with astemizole has been reported to affect children less frequently (96% sedation-free) than adults (84% sedation-free).[20] Substantiating the low affinity of terfenadine and astemizole for cholinergic receptors, anticholinergic-like symptoms (i.e. dry mouth) were infrequently experienced by patients administered either second generation antihistamine.[20,71,74-77] Dry mouth was reported to occur in children and adults receiving therapeutic dosages of astemizole nearly as frequently as patients receiving placebo, approximately 5.0 and 4.5%, respectively.[20,73]

2.4 Antihistamine-Associated Torsades de Pointes

Despite few adverse events being associated with therapeutic dosages of terfenadine and astemizole some patients who accidentally or intentionally ingested normal or excessive doses of terfenadine or astemizole alone or in conjunction with other drugs metabolised by CYP3A4 or, more importantly, agents which inhibit the activity of CYP3A4 (table V), experienced life threatening dysrhythmias including torsades de pointes. In 1989, the first case of torsades de pointes associated with an intentional overdose of terfenadine was described.[79] This was soon followed by other cases occurring in children and adults.[80] From these reports, it was noted[81] that patients exhibiting dysrhythmias had either exceeded the FDA recommended daily dose, taken 1 of these antihistamines concurrently with a drug known to interfere with hepatic CYP3A4 isozyme activity (table V) or had significant underlying liver dysfunction.[82,83]

Table V. Selected drugs which can inhibit cytochrome P450 3A4 isozyme activity[78]

Cimetidine
Citalopram
Diltiazem
Fluconazole
Fluvoxamine
Fluoxetine
Indinavir
Itraconazole
Ketoconazole
Macrolides (erythromycin, clarithromycin)
Metronidazole
Naringenin (active component of grapefruit juice)
Nefazodone
Norfluoxetine
Ritonavir

From these reports, it is unknown if the patients described had an undiagnosed cardiac abnormality such as primary prolonged QT syndrome which might have increased their risk of developing a dysrhythmia with these second generation antihistamines. Nevertheless, it would seem reasonable to believe that a patient with a pre-existing prolonged QT interval or other underlying cardiac abnormality might be predisposed to develop an antihistamine-induced dysrhythmia.

2.5 *In Vitro* Cardiac Electrophysiology Associated with Second Generation Antihistamines

The electrophysiology of both terfenadine and astemizole-induced dysrhythmias has been well described. Terfenadine *in vitro*, has been shown to substantially reduce (and in some cases abolish) the outward potassium-mediated tail current by blockage of the delayed outward rectifier potassium current (I_{Kr}) channels.[84-86] Assessment of the outward potassium-mediated tail current is a highly selective method for measuring outward potassium channels.[84,87] Blocking of the I_{Kr} channels produces a depressed peak in the voltage and a decrease in potassium outflow. Terfenadine, astemizole, and other selected drugs can produce a net imbalance in the influx and efflux of ions predisposing the myocardium to early after depolarisation, which if sizable, may ultimately be observed as a dysrhythmia and most notably torsades de pointes.

Human ventricular myocytes are comprised of 5 different classes of potassium channels. Terfenadine concentrations of >471 μg/L *in vitro* block nearly 100% of all 5 classes of feline potassium channels.[84] Although this *in vitro* concentration[84] far exceeds concentrations clinically observed with use of terfenadine at therapeutic dosages,[84,88] patients who have overdosed or taken concurrent medications which inhibit terfenadine metabolism may experience serum concentrations in excess of 80 μg/L which are consistent with concentrations shown to block 50% of feline and guinea-pig I_{Kr} channels (approximately 70 and 24 μg/L, respectively).[84,85] Salata et al.[85] have confirmed these

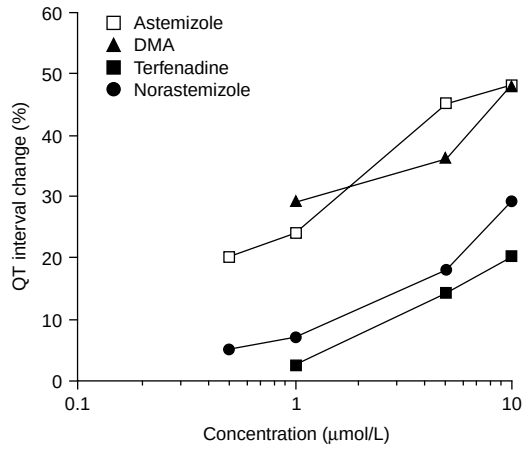

Fig.1. Percentage change in QT interval induced by second generation histamine H_1 receptor antagonists (antihistamines) in cells expressing human ether-a-go-go related genes (HERG). Terfenadine was assessed using feline myocardium and this may therefore explain the larger concentrations needed to induce QT interval changes. Ketoconazole induces QT interval changes when administered alone (data not presented).[7,84] **DMA** = desmethyl astemizole.

observations that terfenadine preferably antagonises the I_{Kr} channel. Furthermore, terfenadine has been observed to block the I_{Kr} channel expressed by the human ether-a-go-go-related gene (HERG)[89] underscoring the potential for terfenadine to induce QT interval prolongation (fig. 1) and dysrhythmias in humans. Albeit at much higher concentrations (e.g. μmol/L), terfenadine has consistently demonstrated blockade of other human cardiac potassium channel targets such as Kv1.5, which express the ultra-rapid outward potassium current (I_{kur}) channel in human atrial tissue.[89] Clinically, terfenadine serum concentrations as low as 7 μg/L have been associated with an increase in the QT_c interval in healthy adults.[90] Even though the serum concentration observed in this patient appeared to be much lower than that reported to block 50% of the potassium channels in myoctes,[84,85] both terfenadine and astemizole concentrate within the myocardium at concentrations approximately 200 to 400 times greater than concentrations reflected in the serum.[91] These data may suggest that the serum concentration for

antihistamines that concentrate within the myocardium (e.g. terfenadine and astemizole) do not accurately predict their propensity to induce cardiac dysrhythmias.

Astemizole, though less well studied than terfenadine, presumably induces torsades de pointes in a similar manner. The primary metabolite of astemizole, DMA, also appears to inhibit I_{Kr} channels in a manner similar to that of astemizole and terfenadine.[68] The remaining astemizole metabolites, norastemizole and 6-HDMA can antagonise I_{Kr} channels, although not as completely as the parent drug or DMA.[92,93] In contrast to terfenadine, no defined correlation has been identified between astemizole serum concentrations and prolongation of the QT interval (fig. 1). Chen and Woosley[92] reported that 10 μol/L of astemizole completely blocked the I_{Kr} channels and approximately 50% of the transient outward potassium channels leading to a prolonged QT interval. The effects of both astemizole and its metabolite DMA together on the action potential or QT interval prolongation have not been examined thus it is not known whether the cardiac effects of the 2 compounds are potentially additive or synergistic.

The manufacturer of norastemizole, one of the active metabolites of astemizole, has recently completed phase 3 clinical trials.[94] It is anticipated that norastemizole will be approved relatively soon for market in the US and elsewhere. Norastemizole is described to increase the QT interval in feline myocardium[92] although the concentration of norastemizole needed to antagonise approximately 50% of I_{Kr} channels and increase the QT interval appears to be substantially greater than astemizole or its major metabolite, DMA.[92,93,95] Norastemizole appears well tolerated at therapeuticdosages. Nevertheless the ability of norastemizole to increase the QT_c interval (fig. 1) suggests norastemizole-intoxicated patients may be at an increased risk for cardiac dysrhythmias, however there is no evidence that this is the case.

The *in vitro* data summarised in this section appear to correlate well with clinical experience. The terfenadine plasma concentration in a woman who experienced torsades de pointes with fatal outcome after receiving terfenadine together with the CYP3A4 inhibitor, ketoconazole (table V), was 0.12 μmol/L (57 μg/L).[84] Woosley et al.[84] found this concentration to be nearly identical to the concentration necessary to block 50% of the I_{Kr} channels in feline myocardium. Thus blockade of I_{Kr} channels in ventricular myocytes with either terfenadine or astemizole, if significant enough, could cause these cells to depolarise early, inducing torsades de pointes.

2.6 Acute Terfenadine and Astemizole Poisoning in Children

Accidental and intentional overdoses with terfenadine and astemizole in children have been well described.[93,96-102] Overdoses of terfenadine and astemizole may produce similar cardiac sequelae in susceptible individuals although adverse effects associated with an overdose of terfenadine are usually observed sooner (i.e. within hours) after ingestion than with astemizole (see table IV). Children who have intentionally or accidentally ingested an overdose of astemizole and present to the emergency department are usually fully conscious[98] or only slightly lethargic[97,101,102] whereas patients ingesting large amounts of terfenadine often presented in a very lethargic or comatose state.

Most importantly, first and second degree atrioventricular (AV) block as well as other cardiac dysrhythmias have been reported commonly[101,102] with both terfenadine and astemizole intoxications. These dysrhythmias have occurred within hours[97,101] to days[100] after ingestion of the overdose with some patients converting to torsades de pointes.[103] Thus, patients who ingest astemizole require continuous close monitoring as they may initially appear completely normal prior to experiencing a potentially life-threatening dysrhythmia as was shown in a report by Broadhurst and Nathan[104] of a young woman with long QT syndrome who experienced a cardiac arrest after ingesting astemizole,[104] as the concentration of the parent compound and metabolite continue to accumulate. Prior to the recognition of astemizole-induced car-

diotoxicity, patients reporting overdoses were often discharged home or admitted to the hospital floor for observation without cardiac monitoring with potentially devastating consequences.[105] Some of these patients experienced unconsciousness and a severe decrease in cardiac output[99,100] possibly related to a ventricular arrhythmia occurring up to 20 hours after ingestion. Intermittent dysrhythmias have also been described, occurring up to 48 hours after astemizole ingestion.[102] Other electrocardiogram (ECG) abnormalities observed in astemizole intoxicated children have included tachycardia and prolongation of the QT interval, which may be evident within hours of the ingestion and last for several days (reported up to 5 days).[93,97,102] This apparent discrepancy in the manifestation of associated symptoms between terfenadine (early) and astemizole (late) would appear to reflect the difference in the 2 drugs' rate of hepatic metabolism to nontoxic and toxic metabolites. Therefore, patients ingesting a potentially toxic amount of astemizole or terfenadine should be admitted to the hospital for intensive cardiac monitoring (see section 5 for recommendations).

In summary, Disruption of cardiac I_{Kr} channels with either terfenadine or astemizole may induce serious cardiac dysrhythmias. Torsades de pointes must be considered a medical emergency requiring prompt medical attention. Patients at risk for serious cardiac adverse effects associated with either terfenadine or astemizole may require continuous ECG monitoring. Following astemizole intoxication monitoring may be required for several days. Presently, the manufacturers of terfenadine and astemizole have removed their respective drugs from a number of markets, including the US. Yet despite the increased awareness, cardiotoxicities associated with terfenadine and astemizole, QT interval prolongation and torsades de pointes associated with both terfenadine and astemizole continue to be reported.[106-108]

3. Third Generation Antihistamines

The recognition of the serious adverse effect potential associated with the administration of the second generation antihistamines focused attention on loratadine and other, newer third generation compounds. These drugs have enjoyed widespread clinical use because of their overall efficacy in treating hyperhistaminic conditions, low propensity to induce sedation (similar to second generation agents) and high degree of safety. Most importantly, the clinical use of third generation agents does not appear to be associated with any adverse including cardiac effects, even in cases of severe overdose.

3.1 Loratadine

Loratadine became available in the US at approximately the same time as terfenadine and astemizole. Because of the timing of its release to clinical medicine, it was initially classified as a second generation antihistamine. However, considering that it is nonsedating and lacks clinically important cardiotoxicity, it is more correctly classified as a third generation antihistamine. As is the case for terfenadine and astemizole, little is known about the pharmacokinetics of loratadine or its major active metabolite, descarboethoxyloratadine (DCL), in children. After absorption into the systemic circulation approximately 97 to 99% and 73 to 76% of loratadine and DCL, respectively, are bound to plasma proteins.[109] Loratadine is distributed extensively into tissues with an apparent volume of distribution of 119 L/kg[110] (table IV).

The metabolic pathway for loratadine differs from that of terfenadine or astemizole. Loratadine is metabolised by the CYP enzyme system via both CYP3A4 and 2D6 isozymes.[111] Inhibition of the primary metabolic pathway of loratadine via CYP3A4 results in a greater dependence upon the CYP2D6 pathway,[111] and vice versa. This parallel metabolism of loratadine appears to markedly reduce the risk of loratadine-associated metabolism based drug-drug interactions. Nevertheless, in our opinion the metabolism of loratadine may be markedly inhibited resulting in accumulation of the parent drug if it is co-administered with selected medications (e.g. nefazodone) which competitively inhibit both CYP3A4 and 2D6 or medication combinations (e.g. erythromycin and fluoxetine) that

could interfere with the activity of both isozymes. Despite this potential for excessive loratadine accumulation, few serious adverse effects, including cardiac toxicity, would be expected to occur (see section 3.1.1).[83,112]

In the vast majority of reported controlled clinical trials, the incidence of loratadine associated adverse events, including sedation, appear to be similar to placebo.[66,113-118] In 1 large placebo controlled study of 271 children with allergic rhinitis aged 6 to 12 years, the incidence of adverse effects in the loratadine group was found to be similar to placebo.[113] Others have confirmed this relative lack of adverse events associated with loratadine administration in children.[114-116] The incidence of sedation associated with either loratadine or terfenadine was similar to placebo, approximately 10, 7, and 8%, respectively, in 317 adult patients experiencing symptoms associated with seasonal allergic rhinitis.[117] Sedation, headaches, and anticholinergic-like effects (i.e. dry mouth) were described by ≤4% of adult patients receiving loratadine,[66,118] which was similar to patients receiving terfenadine or placebo.[117]

3.1.1 Cardiac Effects Associated with Loratadine

In contrast to the second generation antihistamines, astemizole and terfenadine, loratadine appears to lack any clinically important cardiac toxicity. No changes in the action potential or early after depolarisation in the guinea-pig model have been demonstrated.[119] No significant changes in guinea pig ventricular myocyte action potential or surface ECG were observed with loratadine, even with 150 times the normal human dose (on a mg/kg basis) whereas under similar laboratory conditions, terfenadine markedly prolonged the QT interval and induced an arrhythmia resembling torsades de pointes.[119] Blockage of only 20% of guinea-pig potassium channels occurs at a concentration of 2.5 μmol/L loratadine, which is approximately 100 times greater than concentrations achieved when loratadine and ketoconazole are administered concurrently.[88] This is consistent with the data of Woosley and associates,[83] who found no effect of loratadine on cardiac I_{Kr} channels at concentrations up to 10 μmol/L or 875 times those achieved at recommended clinical dosages.

Similar to terfenadine and astemizole, the effects of loratadine on I_{Kr} and human Kv1.5 channels has been evaluated in HERG and Kv1.5 transfected cells. At therapeutic concentrations, loratadine is described to have no effect on human Ikr channels supporting previous experiences described in animals.[66,83] At much higher concentrations (approximately 50 μmol/L) loratadine is estimated to block 50% of HERG I_{Kr} channels.[88] Similar to the animal data, 1 μmol/L of loratadine inhibits approximately 5% of cloned HERG channels expressed in *Xenopus* oocytes.[88] These human *in vitro* findings would appear to support the lack of clinically-induced ventricular dysrhythmias, especially torsades de pointes, observed with loratadine. Nevertheless, at lower concentrations (0.8 to 1.2 μmol/L) loratadine inhibits approximately 50% of human Kv1.5 channels,[120,121] which are primarily found in the atria of the human heart. Furthermore the major metabolite of loratadine, DCL, has also been described to inhibit human Kv1.5 channels at concentrations much higher than the parent drug in voltage, and in a time dependent manner.[121-123] Nevertheless, the concentrations used in these experimental conditions most likely are much greater than those achieved with the recommended clinical dosage or achievable in the situation of clinical overdose/suicide.

Similarly, the co-administration with erythromycin, an effective CYP3A4 inhibitor (table V), and loratadine to healthy adults did not produce any clinically significant prolongation of the QT interval or induce torsades de pointes even though the area under the curve for both parent loratadine and DCL were significantly increased.[112] The relative lack of clinically important adverse events, including cardiac toxicity, with therapeutic and excessive loratadine serum concentrations appears to eliminate any important metabolism-based drug-drug interactions.

3.1.2 Acute Loratadine Poisoning

Unlike terfenadine and astemizole, experience with loratadine intoxication for both children and

adults is very limited and not well described in the literature. Loratadine appears to be well tolerated after overdose substantiating loratadine's selectivity for the H1 receptor and apparent lack of cardiac toxicity. Children administered loratadine at a dosage of more than 10 mg/day experienced only minor adverse effects such as extrapyramidal symptoms and palpitations.[124] Similarly, adults ingesting excessive loratadine doses (40 to 180mg) experienced nonsevere adverse effects such as somnolence, tachycardia, and headaches.[124]

To date there appears to be only 1 reported case in the English language literature describing an apparent arrhythmia associated with loratadine administration. Good et al.[125] described a 69-year-old male who developed nonsustained ventricular tachycardia and a QT_c interval of 476 msec while receiving loratadine 10 mg/day, quinidine 324mg 3 times daily along with other medications. These other medications had not been reported to be associated with torsades de pointes.[125] The authors concluded that the dysrhythmia in this patient was attributable to loratadine administration although they failed to stress the importance of the concurrent administration of quinidine and the patient's previous history of dysrhythmias. It would appear that the dysrhythmias experienced by this patient were more likely associated with causes other than loratadine administration.[83]

3.2 Ebastine, Azelastine, and Mizolastine

Currently not FDA approved in the US, ebastine is available in Europe and a number of other countries around the world. The nonpharmacologically active parent drug, ebastine, is structurally similar to terfenadine and is rapidly and extensively metabolised by CYP3A4 and possibly another unidentified alternative pathway[126,127] to the active metabolite, carebastine. Azelastine, another relatively new nonsedating antihistamine is currently approved in the US and other countries as an intranasal spray (except in Japan where an oral formulation is available). Azelastine is pharmacologically active and is metabolised by CYP3A4 and 2D6 isozymes to its major, active metabolite, desmethylazelastine.[128,129] Similarly, mizolastine, a newer histamine receptor antagonist, is pharmacologically active and is metabolised to inactive metabolites by CYP3A4 and 2C6 isozymes.[14] Both these antihistamines, in addition to their histamine receptor antagonism appear to possess other important pharmacological actions including inhibition of the release of inflammatory mediators by mast cells that may make them useful for the effective relief of asthma-associated symptoms.[130-132]

The co-administration of a known CYP3A4 isozyme inhibitor, (e.g. ketoconazole or erythromycin; see table V), can increase ebastine serum concentrations 10 to 30 times values observed with normal therapeutic dosages.[133-135] Unlike ebastine, the co-administration of azelastine[136] or mizolastine[137] with erythromycin did not produce any significant alteration in the pharmacokinetic profile of either antihistamine. This lack of change in the disposition characteristics of azelastine further supports an alternative metabolic pathway other than CYP3A4.[128,129]

The pharmacokinetics of ebastine, azelastine, and mizolastine are summarised in table IV. There appears to be no difference in the pharmacokinetics of these agents between children and adults. Both ebastine syrup 5mg and 10mg administered to children age 6 to 12 years inhibited the histamine induced wheal and flare for approximately 28 hours thereby suggesting once daily administration is appropriate in children.[138] Once a day administration of ebastine is further supported by the long half-life of carebastine, which appears to be approximately 10 to 14 hours in children.[138] Adverse events associated with ebastine administration appear to be similar to placebo.[138] The most common adverse events described with ebastine administration were headache, somnolence, and dry mouth.[138]

Azelastine has been formulated mainly as a nasal spray that delivers 132μg of drug per actuation although as noted above, an oral formulation is available in Japan. Regulating authorities in some countries have approved paediatric administration of azelastine nasal spray for allergic rhinitis. The lower dose and the topical application of azelastine

would be expected to diminish or circumvent possible systemic adverse events. Rethmuller-Winzen and colleagues[139] observed a mean steady state azelastine concentration of approximately 6- to 8-fold less after 4 intranasal sprays of azelastine compared with an oral dose of 4.4mg in healthy adults even when the dose was normalised. The most common adverse events associated with nasal azelastine were alterations in taste perception and nasal burning. All other adverse events described (e.g. headaches, somnolence, paroxysmal sneezes, dry mouth) were reported at rates similar to placebo.[140]

3.2.1 *In Vitro* and *In Vivo* Cardiac Effects of Ebastine, Azelastine and Mizolastine

The cardiotoxicity profile of ebastine has not been fully described. We were unable to identify any studies describing a relationship between ebastine drug concentration and QT_c interval prolongation. Carebastine 50 mg/kg has been reported to have no effect on QT_c interval in the guinea-pig model therefore it is believed that carebastine, similar to fexofenadine, does not increase the risk of patients developing ventricular dysrhythmias receiving the parent drug, ebastine.[141] In rats receiving intravenous ebastine 3 mg/kg, the maximal QT_c interval prolongation observed was approximately 4 msec whereas with greater than 3 times the 'therapeutic' dose (10 mg/kg) the maximal increase in QT_c interval was 9.7 msec.[142] Furthermore, there was a 4-fold difference in the respective serum concentrations obtained suggesting a possible nonlinear or saturable relationship between QT_c interval and serum concentrations.[142] Ko and colleagues[143] describe the ability of ebastine to block I_{Kr}, and other potassium channels in the rat, guinea-pig, and HERG model. These authors demonstrated approximately 72% inhibition of I_{Kr} channels in guinea-pig ventricular myocytes with concentrations of ebastine approximately 235 times greater than steady state concentrations observed in patients receiving clinically acceptable ebastine dosages of 20 mg/day for 7 days.[61] In *X. leavis* oocytes expressing human HERG I_{Kr} channels, approximately 1.4 μg/ml of ebastine inhibited 46% of the current.[143] This concentration is approximately 235 times greater than usually achieved therapeutic peak serum concentrations observed in healthy adults[61] and approximately 26 times greater than those observed in patients receiving concurrent CYP3A4 inhibitors (e.g. erythromycin and ketoconazole).[138] Thus, the likelihood of achieving such high concentrations resulting in clinically apparent cardiotoxicity with the clinical use of ebastine, is unlikely similar to loratadine.

In children receiving ebastine 1 to 10 mg/day, 3.5% of 202 of these children had a QT_c interval increase of greater than 15% over baseline.[91] Similar to the paediatric data, only 1.9% of 842 adults receiving ebastine 1 to 30 mg/day had a QT_c interval increase greater than 15% above baseline which, in both cases, was similar to that observed with placebo.[91] In 1 study, healthy adults were administered placebo, ebastine 60 or 100 mg/day (3 to 10 times the normal therapeutic dosage) or terfenadine 180mg twice daily (3 times the recommended dosage) for 7 days.[135] The patients who received ebastine 60 mg/day had similar QT_c interval changes as placebo whereas patients receiving ebastine 100 mg/day experienced a significant QT_c interval increase (10.3 msec) compared with placebo. Although these patients experienced a prolongation of the QT_c interval, it was significantly less then patients receiving terfenadine and believed not to be of any clinical significance.[135] These findings are consistent with other studies.[91,144]

Little data are available about the possible cardiac events associated with azelastine. Data on file with the drug's manufacturer suggest that azelastine has no effect on prolongation of the QT_c interval.[145] Furthermore, clinical studies of azelastine has failed to describe any clinically significant cardiac adverse events.[130,131,140,146-149] Similarly clinical studies with mizolastine have failed to describe any clinically significant cardiac adverse events.[137,150]

After an exhaustive search, we were unable to uncover any published descriptions of ebastine, azelastine or mizolastine intoxication occurring in

either children or adults. It would appear that ebastine does not increase the QT_c interval except at extremely elevated concentrations. Nevertheless one must be cautious in the interpretation of these data as it was nearly 10 years after the first marketing of terfenadine before torsades de pointes was first reported with its use. However, the lack of inhibition of potassium channels *in vitro* and in animal models, except at supratherapeutic concentrations combined with the lack of any clinical reports/findings may suggest the safety of ebastine when administered to the general population. More experience is clearly needed to fully elucidate the drug's overall cardiac safety profile.

3.3 Fexofenadine

The second third generation antihistamine to be marketed in the US was fexofenadine or terfenadine carboxylate, the active metabolite of terfenadine. This compound is also available in other major markets. The parent compound, terfenadine, possesses no desirable therapeutic effects until hepatically metabolised via CYP3A4 to the active metabolite fexofenadine. In the absence of concurrent administration of an inhibitor of hepatic CYP3A4 (table V), overdoses, or administration of the drug to patients with marked hepatic dysfunction, terfenadine is rapidly converted to fexofenadine, which is responsible for all of the antihistaminic effects of terfenadine. Since terfenadine is the prodrug of fexofenadine, the clinical efficacy of fexofenadine would not be expected to differ from that of published reports for terfenadine.

At present fexofenadine is not labelled in the US for use in children under the age of 12 years. Although several clinical studies of fexofenadine in children are ongoing, no published data are yet available. In assessing the clinical pharmacology of fexofenadine in paediatric patients, Simons et al.[64] performed a double blind two-way crossover study in 14 children (mean age of 9.8 ± 1.8 years). The half-life of fexofenadine in these children was approximately 18.0 hours and the volume of distribution was approximately 5.8 L/kg after a 60mg dose. The fexofenadine half-life in children in this study[64] did not differ substantially from data reported in adults (14 hours).[151] Careful inspection of the data of Simons et al.[64] suggests that the reported fexofenadine half-life may be in error because of the sparse blood sampling strategy used by the investigator, which may have overestimated the true elimination half-life in children. Nevertheless, the children in this study were found to experience no serious adverse effects and ECGs were normal in all patients.[64]

Fexofenadine has been well tolerated even at doses exceeding the recommended therapeutic dosage (see section 3.6) The most common adverse effect associated with fexofenadine administration in adults was headache observed in 1.4 to 3.4% of patients receiving the drug. In 1 comparative trial[151] assessing the safety and efficacy of fexofenadine, cetirizine and placebo, the incidence of headaches was the same (8, 8 and 7%, respectively) suggesting that headaches may be associated with the underlying medical conditions of patients rather than use of their prescribed antihistamines.

3.4 Cetirizine

Soon after the clinical availability of fexofenadine, cetirizine, which is less sedating than first generation antihistamines and noncardiotoxic, was marketed in the US. Cetirizine has been extensively used in Europe for many years. Cetirizine, a zwitterion and potent H_1 receptor antagonist, is the carboxylated metabolite of hydroxyzine. Once absorbed, it is bound in serum primarily to albumin.[152] Similar to fexofenadine, cetirizine is not metabolised by the liver, with greater than 60% of unchanged drug excreted from the body via the kidney[153] by an active transport mechanism.[154] The pharmacokinetics of cetirizine in children has been described (table IV). The elimination half-life of cetirizine appears to vary with age. The elimination half-life of approximately 7.0 hours[56,57] in children 8 to 10 years of age appears to be similar to that reported in healthy adults (approximately 7.4 to 8.6 hours).[57,153] In infants and toddlers with an average age of 12.3 months, the half-life of cetirizine was much more rapid, and highly variable rang-

ing from 0.8 to 6.5 hours (mean 3.1 hours).[58] Although infants have a shorter half-life and more rapid body clearance than older children and adults, the wheal and flare response is adequately suppressed for up to 12 hours after receiving usual doses regardless of age suggesting substantial tissue concentrations of cetirizine.[58]

Unlike fexofenadine, the most common adverse effect associated with cetirizine appears to be sedation. Data obtained from the drug's manufacturer suggest the incidence of drowsiness in patients treated with cetirizine is approximately twice that of fexofenadine and placebo (6 *vs* 3 and 3%, respectively).[155] Cetirizine appears to be much less sedating than its parent compound, hydroxyzine but possibly more sedating than loratadine or fexofenadine.[155] Nevertheless, the overall incidence of sedation requiring discontinuation of therapy in children 6 years of age and older is only approximately 1%[155] and is similar to rates observed with other nonsedating antihistamines (see table II). The most common cetirizine-associated adverse events reported in children ages 6 to 11 years were abdominal pain and sedation whereas older children did not describe abdominal discomfort as frequently.[155]

3.5 *In Vitro* and *In Vivo* Cardiac Effects of Fexofenadine and Cetirizine

Under experimental conditions, fexofenadine appears to be devoid of any cardiac toxicity. This is in clear contrast to its parent compound, terfenadine, or the other second generation antihistamine, astemizole. Fexofenadine serum concentrations approximately 32 times greater than those achieved with usual therapeutic administration had little effect on guinea-pig I_{Kr} channels[151] appearing almost identical to control cardiac I_{Kr} tails.[84] *In vitro*, fexofenadine is 583 times less potent in blocking guinea-pig cardiac I_{Kr} channels than terfenadine[93] suggesting that fexofenadine is virtually devoid of cardiac effects under therapeutic and excessive dose conditions.

Similar to fexofenadine, cetirizine has been described to be clinically devoid of inhibiting potassium channels. At concentrations of 30 μmol/L and less, cetirizine had no effects on HERG I_{Kr} channels.[156] These results supported the findings of Carmaliets[157] that approximately 50% of guinea-pig I_{Kr} channels were inhibited at concentrations of 100 μmol/L of cetirizine which is approximately 150 times greater than that observed after 10mg of cetirizine orally. The lack of inhibition of I_{Kr} channels *in vitro*, further supports the lack of clinical QT interval prolongation in patients receiving cetirizine.

Several clinical studies have attempted to uncover possible severe adverse events associated with therapeutic or supratherapeutic doses of either cetirizine or fexofenadine. No clinically significant ECG changes have been observed when children were administered either cetirizine or fexofenadine.[158] Administration of therapeutic doses of cetirizine 5mg or 10mg to 119 children aged 6 to 11 years did not produce any appreciable prolongation of the QT interval on a surface ECG obtained on days 1 and 11 to 17 of therapy.[158] Most children (more than 80%) receiving either 5mg or 10mg of cetirizine had a QT interval change of less than 5% from baseline.[158] The absence of cetirizine-induced QT interval prolongation was also confirmed in a study of 25 healthy adult men (mean age 28 years) receiving either cetirizine 20 or 60 mg/day for 7 days.[159]

Similar to children receiving therapeutic doses of cetirizine, administration of high doses of fexofenadine (e.g. 10 to 800mg) to healthy adults did not appear to significantly affect the QT interval as compared with baseline ECG.[160] Prolongation of the QT interval was not observed in adults even when fexofenadine serum concentrations exceeded 6380 μg/L or approximately 14 times greater than the fexofenadine serum concentration observed with therapeutic dosages.[160] Although no serious adverse events were reported with fexofenadine administration, approximately 54% of these adult patients experienced at least 1 minor adverse event with headache and sedation/lethargy being the most common (29 and 17%, respectively).[160]

The lack of any severe adverse events and cardiac dysrhythmias in the clinical studies reflect the

relative *in vitro* cardiac safety of both cetirizine and fexofenadine. These *in vitro* and *in vivo* results suggest that similar to loratadine, few adverse events would be observed clinically in intentional and unintentional cetirizine or fexofenadine intoxications.

3.6 Acute Intoxication Associated with Fexofenadine or Cetirizine in Children

Clinical experience related to accidental/intentional overdoses with fexofenadine or cetirizine in either children or adults has been very limited. An exhaustive review of the literature revealed descriptions of 2 accidental cetirizine ingestions (only 1 published in English)[161,162] and 1 unintentional overdose of fexofenadine.[163] Ridout and Tariq[161] described an 18-month-old child who accidentally ingested 18 ml of cetirizine solution (approximately 13.0 mg/kg). The child was admitted to the hospital where vomiting was induced approximately 75 minutes after the ingestion. Overnight, the child became hyperactive though all vital signs including, blood pressure and cardiac monitoring remained normal.[161] This child was discharged home the next day without sequelae. This case appears to reflect the anticipated safety of cetirizine even when an infant ingests up to 51 times the usual therapeutic dose. Hansen and Feilberg Jorgensen[162] described a 4-year-old baby boy who unintentionally ingested 60mg (3 mg/kg) of cetirizine. As this case report was published in Danish we were only able to evaluate the English translated abstract. Approximately 1.5 hours after the ingestion the patient apparently experienced severe lethargy and vomiting was induced. His ECG remained normal the entire time he was observed and he was later discharged without further sequelae.

As with cetirizine there are few descriptions of adverse events occurring after supratherapeutic doses of fexofenadine. Pinto et al.[164] describes a 67-year-old man with pre-existing cardiac abnormalities (left ventricular hypertrophy and prolonged QT interval) who experienced an increased prolongation in his QT interval after ingesting 180mg of fexofenadine. The patient was rechallenged 6 days later in the hospital and was described to experience an increase of his QT interval and ventricular tachycardia, which progressed to ventricular fibrillation. The manufacturer of fexofenadine reported in their response to this case description that the patient had pre-existing cardiac disease, pre-existing QT prolongation, and that the patient refused treatment with an implantable defibrillator.[163] The manufacturer of fexofenadine also noted that the patient experienced an in-hospital episode of ventricular tachycardia during a fexofenadine free period although this description was not clear from the published case report.[163] Despite the interpretive challenge of the case report by the manufacturer[163] the authors of the original case report strongly disagree with the manufacturer's assessment of their case assessment and reiterate their belief that the arrhythmias observed in their patient were directly related to fexofendine administration.[165] Although the exact mechanism(s) of the arrhythmias observed in this patient may not be clear and the possibility of their relationship with fexofenadine administration disputed, this report underscores the importance of postmarketing surveillance for identifying possible drug-induced adverse effects. However, based upon the data from the above safety studies and the possible discrepancies in this single case report, the cardiotoxic potential of fexofenadine would appear to be extremely small.

In an attempt to better quantify the magnitude and extent of fexofenadine and cetirizine associated adverse effects, we requested, received and critically reviewed all adverse events reported to the FDA Adverse Event Reporting System (AERS) programme for loratadine, fexofenadine, and cetirizine as of July 2, 1999. Since the release of loratadine, fexofenadine, and cetirizine in the US, the FDA has received 1375, 1322 and 542 case reports of patients experiencing adverse events associated with these agents, respectively. Health care workers and patients themselves throughout the world prepared the descriptions of these adverse events. Interpretation of these data must be undertaken cautiously since these descriptions submitted

Table VI. Adverse events associated with fexofenadine administration commonly reported to the US Food and Drug Administration (FDA) Adverse Event Reporting System[a]

Adverse event	No. of patients	% of total
Total number of case reports reviewed[b,c]	547	
Anticholinergic-like effects	76	13.9
constipation	3	
diarrhoea	11	
dysuria	9	
headaches	16	
sedation	34	
Convulsions	17	3.1
possible pre-existing epileptic condition[d]	3	
Dizziness	18	3.3
Dysrhythmias	109	19.9
atrial dysrhythmia	19	
atrioventricular	2	
bradycardia	4	
nonspecific dysrhythmia	28	
QT prolongation	6[e]	
tachycardia[f]	39	
ventricular dysrhythmias	11	
Hypersensitivity	14	2.6
Elevated liver function tests	13	2.4
Nausea and vomiting	20	3.7
Palpitations	21	3.8

a Report of an adverse event to the FDA Adverse Event Reporting System, a voluntary reporting system, does not constitute causality.

b More than one report may be submitted to the FDA.

c Patients may report more than one adverse event.

d Patients receiving concurrent antiseizure medication.

e Some patients receiving known medications to prolong the QT interval.

f Possibly associated with anticholinergic-like effects.

to the FDA may not reflect causality or even a possible relationship with the drug. In reviewing these data we attempted to delete all duplicated descriptions of the same patients and adverse events although unique patient identifiers were removed making this process difficult. The most commonly reported adverse events to the FDA via the AERS are presented in tables VI, VII, and VIII. Inspection of these reports failed to identify any trends in the type or incidence of reported adverse effects. Close examination of these reported adverse events reveals that the several described adverse events appear to be associated with a previous medical condition (e.g. seizures experienced by a person with known epilepsy) or other possible medications [e.g. increased heart rate experienced by a patient receiving salbutamol (albuterol)]. Moreover there appears to have been only a few overdoses and few reported serious cardiac toxicities associated with the use of these medications.

4. Learning and Performance Effects of the Second and Third Generation Antihistamines

Treatment and nontreatment of symptoms associated with hyperhistaminic conditions has been associated with decreased performance and learning. Performance capability and learning for both children and adults appears to be affected less by the administration of a second or third generation antihistamines compared with similar patients receiving first generation antihistamines or placebo. A single dose of terfenadine,[166,167] loratadine[168] or cetirizine[169-171] appears to have a similar effect to placebo in inducing substantially less daytime sleepiness when compared with treatment with first generation antihistamines. As stated previously, other authors have described a slight increase in the incidence of cetirizine-associated sedation compared with terfenadine or loratadine.[172,173] Overall, a lack of sedation has been described with both subjective and objective measurements for all the second and third generation antihistamines. As described above (see section 1.2) the term sedation encompasses more than just a soporific effect of the drug. Many of these drugs do not induce sleepiness although other aspects of psychomotor response many be impaired.

Only a few second and third generation antihistamines have repetitively demonstrated no sedative properties in either volunteer or in patients experiencing a hyperhistaminic condition. Astemizole, ebastine, and fexofenadine at therapeutic and supratherapeutic doses did not appear to lead to any clinically important impairment of psychomotor performance, sensorimotor, memory, motor and physiological activity.[16] Furthermore, patients re-

ceiving these antihistamines did not subjectively rate themselves as being sedated or impaired.

As stated above, most second and third generation antihistamines induce substantially less sedation than first generation agents although the newer antihistamines are not completely devoid of sedative effects. Cetirizine at dosages greater than 2.5 mg/day has been described to impair sensorimotor speed and patients have subjectively rated themselves as being impaired.[16] Both loratadine and mizolastine, mostly at dosages greater than 20 mg/day, have been described to impair psychomotor, sensorimotor speed, sensory skills.[16] Furthermore, patients and volunteers self-rated themselves as being sedated when receiving more than 20mg of loratadine or mizolastine.[16] Terfenadine at a dose of 60mg has been described to impair patients psychomotor performance, sensorimotor, CNS arousal, memory, and physiological response and, furthermore, at high doses patients have subjectively reported impairment.[16] Clearly, even though these second and third generation antihistamines do not appear to induce sleepiness, many of these antihistamines can impair other psycho/motor responses to varying degrees.

The relative lack of sedative effects associated with loratadine and fexofenadine is thought to translate into better learning performance and decreased negative impact on other activities. Therapeutic dosages of first generation antihistamines, particularly diphenhydramine and hydroxyzine, have been described to adversely affect cognitive and psychomotor performance.[8-12,39,39,174]

The second and third generation antihistamines appear to improve cognitive and psychomotor performance when compared with first generation antihistamines or placebo yet rarely produce the same level of cognitive and psychomotor performance to that observed in healthy, nonsymptomatic patients.[175-178] Children with allergic rhinitis between 10 to 12 years of age had substantially improved learning after administration of loratadine 10mg/day when compared with either placebo or diphenhydramine 25mg twice daily yet remained inferior to healthy children.[8] Confirming this experience in paediatric patients, cognitive function was unimpaired in adults administered a single dose of loratadine 10mg.[118,170,171,175] Differences in psychomotor and cognitive performance in patients receiving loratadine and diphenhydramine appears to become clinically nonsignificant after 3 to 5 days of therapy[168] yet sedation continues to be subjectively described by many patients receiving diphenhydramine.

Terfenadine,[166,175,176] astemizole,[177] fexofenadine[178] and cetirizine[175] have all been described

Table VII. Adverse events associated with cetirizine administration commonly reported to the US Food and Drug Administration (FDA) Adverse Event Reporting System[a]

Adverse event	No. of patients	% of total
Total number of case reports reviewed[b,c]	1338	
Accidents (e.g. motor vehicle)	10	0.8
Anticholinergic-like effects	254	19.0
constipation	29	
diarrhoea	11	
dry mouth	33	
headaches	49	
sedation	132	
Convulsions	34	2.5
possible pre-existing epileptic condition[d]	8	
Dizziness	41	3.1
Dysrhythmias	100	7.6
atrial dysrhythmia	9	
atrioventricular	3	
nonspecific dysrhythmias	24	
QT prolongation	8[e]	
tachycardia[f]	48	
ventricular dysrhythmias	8	
Hallucinations/agitation	43	3.3
Hypersensitivity	44	3.3
Elevated liver function tests	31	2.3
Nausea and vomiting	29	2.2
Palpitations	21	1.6

a Report of an adverse event to the FDA Adverse Event Reporting System, a voluntary reporting system, does not constitute causality.

b More than one report may be submitted to the FDA.

c Patients may report more than one adverse event.

d Patients receiving concurrent antiseizure medication.

e Some patients receiving medications known to prolong the QT interval.

f Possibly associated with anticholinergic-like effects.

to increase psychomotor and cognitive performance compared with first generation antihistamines. In 1 study, the driving ability of 24 healthy adults receiving fexofenadine was compared with clemastine and placebo.[178] On days 1 and 4 patients receiving clemastine 2mg twice daily, a first generation antihistamine, did significantly worse driving than patients receiving placebo ($p < 0.05$ or < 0.01) whereas all patients receiving fexofenadine (60mg twice daily, 120 mg/day, 120mg twice daily, or 240 mg/day) showed no driving impairment. Interestingly, the driving performance of patients who were receiving fexofenadine 120mg twice daily was significantly better than placebo ($p < 0.05$). Although these authors described no driving impairment in patients receiving fexofenadine, patients who received either fexofenadine 120 mg/day or 240 mg/day did significantly worse with their choice reaction time ($p < 0.05$). O'Hanlon and Ramaekers[179] reviewed 9 studies assessing the driving abilities of patients after receiving first generation and second generation antihistamines. Patients receiving terfenadine, loratadine or ebastine did not experience any driving impairment unless they were administered 2 to 3 times the daily dose. Nevertheless, these patients experienced less effect upon their driving ability than patients receiving first generation antihistamines.

Loratadine and fexofenadine with their lack of sedation and decreased effect in psychomotor and cognitive function may be an appropriate choice for school age children experiencing symptoms associated with hyperhistaminic conditions and necessitating antihistamine therapy. Nevertheless, evaluations of the possible impact of fexofenadine and cetirizine may have on a child's learning and/or cognitive function requires specific study.

Table VIII. Adverse events associated with loratadine administration commonly reported to the US Food and Drug Administration (FDA) Adverse Event Reporting System[a]

Adverse event	No. of patients	% of total
Total number of case reports reviewed[b,c]	1412	
Alopecia	20	1.4
Anticholinergic-like effects	167	11.8
constipation	5	
diarrhoea	12	
dry mouth	32	
headaches	51	
migraines	3	
sedation	65	
Chest pain (nonspecific)	25	1.8
Confusion	14	1.0
Convulsions	30	2.1
possible pre-existing epileptic condition[d]	4	
Dizziness	52	3.7
Dysrhythmias	164	11.6
atrial dysrhythmia	12	
atrioventricular block	6	
nonspecific dysrhythmia	11	
nonspecific ECG changes	8	
QT prolongation	15[e]	
tachycardia[f]	67	
ventricular dysrhythmias	19	
ventricular fibrillation	9	
Dysphagia	30	2.1
Palpitations	60	4.3
Syncope	24	1.7
Taste disturbances	18	1.3
Urinary retention	12	0.9

a Report of an adverse event to the FDA Adverse Event Reporting System, a voluntary reporting system, does not constitute causality.

b More than one report may be submitted to the FDA.

c Patients may report more than one adverse event.

d Patients receiving concurrent antiseizure medication.

e Some patients receiving medications known to prolong the QT interval.

f Possibly associated with anticholinergic-like effects.

5. Treatment Recommendations for Overdoses Involving Antihistamines

With increasing awareness of the benefits of treating symptoms associated with hyperhistaminic conditions the clinician may potentially encounter an increased incidence in the number of toxic ingestions involving second and third antihistamines. Treatment of paediatric or adult patients who accidentally or intentionally ingest a large quantity of a first, second or third generation antihistamines is clearly dependent upon the particular antihistamine ingested, the amount ingested and any potential underlying diseases the patient may have (figs 2 and 3). In the US, the incidence of terfenadine or

astemizole ingestions should dramatically decrease since these drugs have been voluntarily removed from the market. Despite the absence of these antihistamines in the US, children and adults in other countries may possibly be exposed to astemizole and terfenadine. Ingestions of these antihistamines in excess of twice the recommended dosage requires the patient to be examined by a physician even if the patient appears to be asymptomatic (fig. 2). Children suspected of ingesting terfenadine or astemizole should undergo an ECG and be admitted to the intensive care unit for further cardiac monitoring. Cardiac abnormalities may occur within 2 to 3 hours after ingesting terfenadine whereas cardiac abnormalities may take longer to manifest with astemizole. If after approximately 12 and 24 hours of ingesting terfenadine or astemizole, respectively, patients are asymptomatic and no ECG changes noted, the patient may be discharged safely. Children with prolonged QT intervals or other ECG abnormalities should remain in the intensive care unit for continuous cardiac monitoring. Cardiac monitoring should continue until the QT interval normalises which may average approximately 12 and 48 hours post ingestion for terfenadine and astemizole, respectively. If prolongation of the QT interval degrades to ventricular tachycardia or torsades de pointes immediate treatment must be instituted.[180] The extremely large apparent volume of distribution and high protein binding of terfenadine, astemizole, and its metabolites preclude the use of extracorporeal measures to enhance the elimination from blood in severely intoxicated patients. Similarly, repeat doses of activated charcoal would be expected to be of limited benefit once terfenadine or astemizole has been absorbed into systemic circulation.

The third generation antihistamines, loratadine, fexofenadine, ebastine, azelastine, mizolastine, and cetirizine are much better tolerated by patients who ingest large amounts. Children who accidentally ingest large quantities of these third generation antihistamines may be adequately managed at home (fig. 3). If the patient is alert, syrup of ipecac or activated charcoal (1 g/kg) should be administered. Patients who have taken an overdose of a third generation antihistamine should be observed for sedative effects and discouraged form performing major activities (e.g. sports, bike riding, driving, etc.) for several hours to avoid possible sedation-induced trauma. Patients who ingest greater than 3 to 4 times the usual daily dose of these third generation antihistamines, especially cetirizine, should be monitored for excessive sedation and other possible anticholinergic effects for approximately 2 to 3 hours after ingestion.

6. Conclusions

For decades, antihistamines have been widely used in clinical practice. Early analogues, including diphenhydramine, pyrilamine and many others (see table I) provided highly effective therapy for most of the bothersome symptoms associated with hyperhistaminic conditions. Unfortunately, the use of these first generation compounds was associated with a substantial degree of drug-induced sedation and interference with a patient's performance of routine tasks. Although these drug-induced adverse effects were often not serious, their common incidence severely limited the clinical utility of these agents fostering the development of newer, nonsedating analogues. Second generation analogues were equally as effective as first generation agents in controlling symptoms associated with hyperhistaminic conditions, but their inherent cardiotoxicity, particularly in overdose, limited their use and ultimately their removal from the market in many countries. Third generation compounds afford the highly desirable nonsedating characteristics of second generation agents without apparent inherent serious adverse effects while maintaining the clinical effectiveness of previous generations.

Accidental/intentional intoxication with first generation antihistamines is unfortunately often associated with serious adverse effects including anticholinergic psychosis, seizures, and possibly coma (table I). In contrast, severe cardiac sequelae including torsades de pointes has been associated with excessive doses, or impaired metabolism with therapeutic doses of second generation antihista-

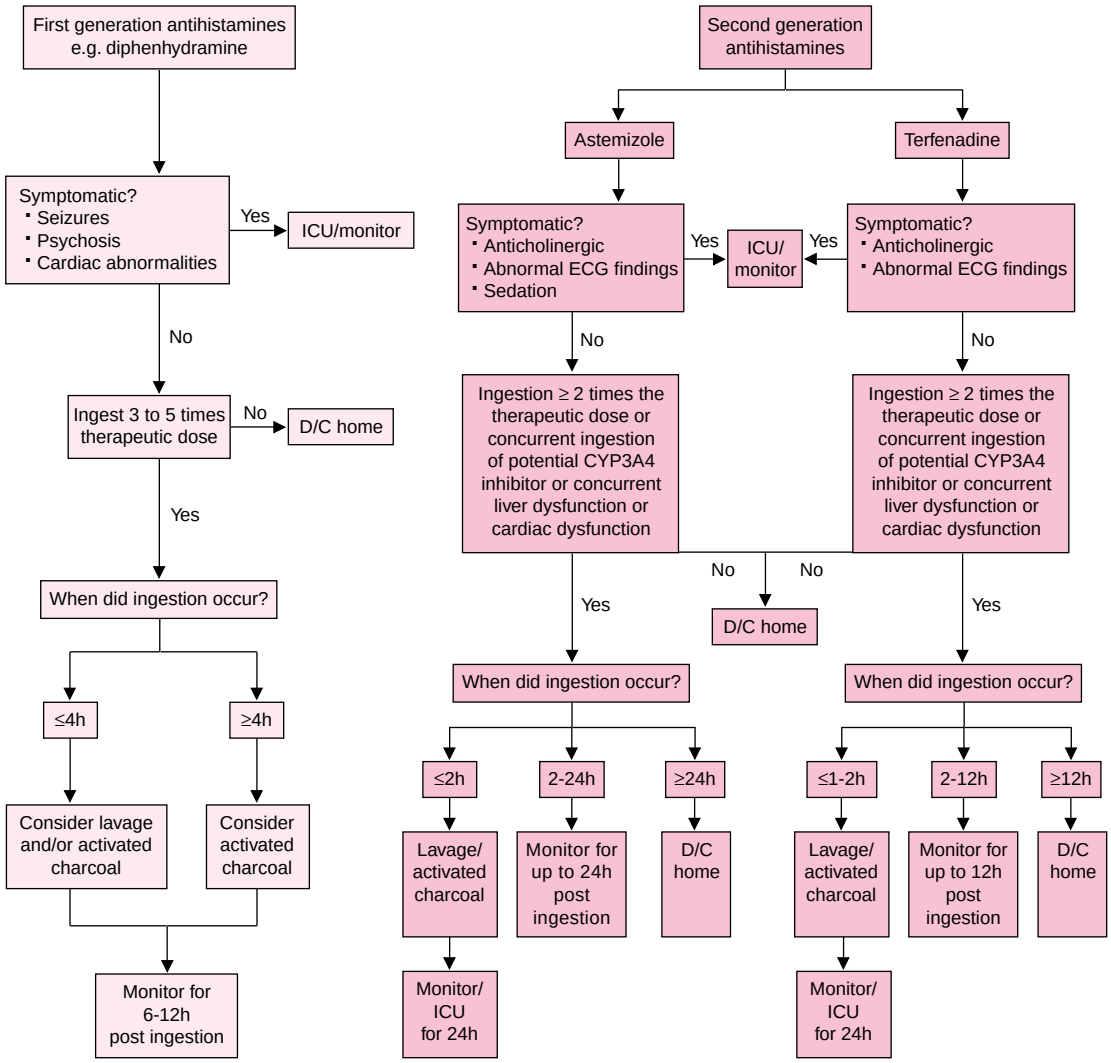

Fig. 2. Therapeutic algorithm for ingestion of first generation (classical) and second generation histamine H_1 receptor antagonists (antihistamines). **CYP** = cytochrome P450; **D/C** = discharge; **ECG** = electrocardiogram; **ICU** = intensive care unit.

mines. More specifically, adverse cardiac effects associated with terfenadine and astemizole have occurred in patients with increased serum concentrations following overdose, use in patients with hepatic dysfunction, or as a result of metabolic drug-drug interactions [e.g. concurrent administration of CYP3A4 inhibitors (table V)]. These serious and potentially life-threatening cardiac toxicities of terfenadine and astemizole underscore the need for hospitalisation and close patient monitoring including detailed evaluation of the ECG focusing on the QT interval (fig. 2). The long elimination half-life of astemizole (e.g. 9 days) suggests that normalisation of the QT interval can be delayed up to several days after astemizole ingestion whereas normalisation of the QT interval would be ex-

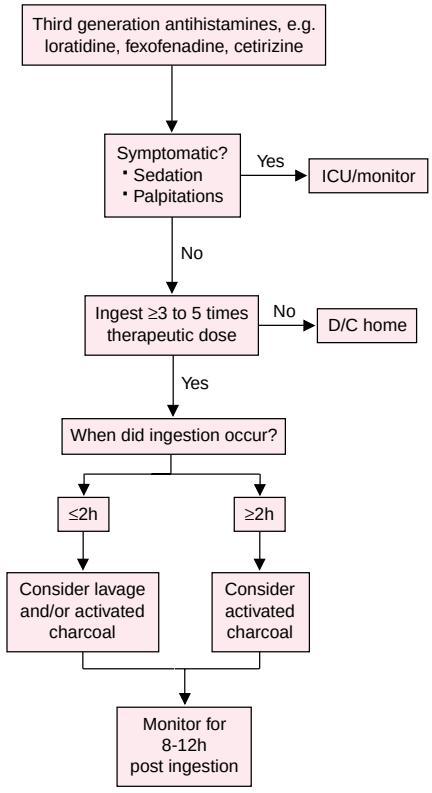

Fig. 3. Therapeutic algorithm for ingestion of third generation histamine H_1 receptor antagonists (antihistamines). **D/C** = discharge; **ICU** = intensive care unit.

pected to occur more quickly after terfenadine intoxication. Although terfenadine and astemizole has been withdrawn from the US market, both these drugs appear to pose a substantial risk to paediatric patients while they are still available in household medicine cabinets and in some countries. Third generation antihistamines including loratadine, fexofenadine, ebastine, mizolastine and cetirizine, appear to be much safer compounds with therapeutic or excessive doses and all lack any associated cardiotoxicities. These medications, even after excessive doses leading to extremely high serum concentrations have not been observed *in vitro* to induce substantial toxicities including torsades de pointes. Intoxication with these third generation antihistamines, especially cetirizine, may be primarily associated with sedation though few adverse events have been reported in patients overdosed with these medications (table III). Thus, it would appear that ingestions of loratadine, fexofenadine, ebastine, mizolastine and cetirizine in children do not require hospitalisation or treatment beyond gastrointestinal decontamination and home observation.

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References

1. Handley D, Magnetti A, Higgins A. Therapeutic advantages of third generation antihistamines. Exp Opin Invest Drugs 1998; 7: 1045-54
2. Mechanisms of antihistamines [discussion]. Clin Exp Allergy 1999; 29 Suppl. 3: 37-8
3. Richards DM, Brogden RN, Heel RC, et al. Astemizole. A review of its pharmacodynamic properties and therapeutic efficacy. Drugs 1984; 28 (1): 38-61
4. McTavish D, Goa K, Ferrill M. Terfenadine: an updated review of its pharmacological properties and therapeutic efficacy. Drugs 1990; 39: 466-74
5. Sorkin EM, Heel RC. Terfenadine. A review of its pharmacodynamic properties and therapeutic efficacy. Drugs 1985; 29 (1): 34-56
6. Simons F. Non-cardiac adverse effects of antihistamines (H1-receptor antagonists). Clin Exp Allergy 1999; 29 Suppl. 3: 125-32
7. Flower F, Araujo O, Nieves C. Antihistamines. Int J Dermatol 1986; 25: 224-31
8. Vuurman EF, van Veggel LM, Uiterwijk MM, et al. Seasonal allergic rhinitis and antihistamine effects on children's learning. Ann Allergy 1993; 71 (2): 121-6
9. Arrighi H, Maiser W, Redding G, et al. The impact of allergic rhinitis in Seattle school children [abstract]. J Allergy Clin Immunol 1995; 95: 192
10. Simons FE. Learning impairment and allergic rhinitis. Allergy Asthma Proc 1996; 17 (4): 185-9
11. Simons FE, Reggin JD, Roberts JR, et al. Benefit/risk ratio of the antihistamines (H1-receptor antagonists) terfenadine and chlorpheniramine in children. J Pediatr 1994; 124 (6): 979-83
12. McLoughlin JA, Nall M, Berla E. Effect of allergy medication on children's reading comprehension. Allergy Proc 1990; 11 (5): 225-8
13. Simons F, Simons K. H1 Receptor antagonists: clinical pharmacology and use in allergic disease. Pediatr Clin North Am 1983; 30 (5): 899-914
14. Simons FE, Simons KJ. Clinical pharmacology of new histamine H1 receptor antagonists. Clin Pharmacokinet 1999; 36 (5): 329-52
15. Nolen TM. Sedative effects of antihistamines: safety, performance, learning, and quality of life. Clin Ther 1997; 19 (1): 39-55; discussion 2-3

16. Hindmarch I, Shamsi Z. Antihistamines: models to assess sedative properties, assessment of sedation, safety and other side-effects. Clin Exp Allergy 1999; 29 Suppl. 3: 133-42
17. Monroe EW, Bernstein DI, Fox RW, et al. Relative efficacy and safety of loratadine, hydroxyzine, and placebo in chronic idiopathic urticaria. Arzneimittel Forschung 1992; 42 (9): 1119-21
18. Monroe EW. Relative efficacy and safety of loratadine, hydroxyzine, and placebo in chronic idiopathic urticaria and atopic dermatitis. Clin Ther 1992; 14 (1): 17-21
19. Harvey RP, Comer C, Sanders B, et al. Model for outcomes assessment of antihistamine use for seasonal allergic rhinitis. J Allergy Clin Immunol 1996; 97 (6): 1233-41
20. Vanden Bussche G, Rombaut N, Schuermans V, et al. Clinical activity of astemizole. A review of world wide data. In: Astemizole: a new nonsedative, long-acting H1 antagonist. Oxford: Medical Education Service, 1984: 101
21. Diffley D, Tran V, Snyder S. Histamine H1 receptors lavelled invivo: antidepressant and antihistamine interactions. Eur J Pharmacol 1980; 64: 177-81
22. Mochizuki T, Yamatodani A, Okakura K, et al. Circadian rhythm of histamine release from the hypothalamus of freely moving rats. Physiol Behav 1992; 51 (2): 391-4
23. Monti JM. Involvement of histamine in the control of the waking state. Life Sci 1993; 53 (17): 1331-8
24. Orr E, Quay WB. Hypothalamic 24-hour rhythms in histamine, histidine, decarboxylase and histamine-N-methyltransferase. Endocrinology 1975; 96 (4): 941-5
25. Leurs R, Blandina P, Tedford C, et al. Therapeutic potential of histamine H3 receptor agonists and antagonists. Trends Pharmacol Sci 1998; 19 (5): 177-83
26. Reiner PB, Kamondi A. Mechanisms of antihistamine-induced sedation in the human brain: H1 receptor activation reduces a background leakage potassium current. Neuroscience 1994; 59(3): 579-88
27. Arrang JM, Garbarg M, Tsien R, et al. Autoinhibition of brain histamine release by a novel class (H3) of histamine receptor. Nature 1983; 302: 832-7
28. Endou M, Levi R. Histamine in the heart. Eur J Clin Invest 1995; 25 Suppl. 1: 5-11
29. Schlicker E, Werthwein S, Zentner J. Histamine H3 receptor-mediated inhibition of noradrenaline release in the human brain. Fundam Clin Pharmacol 1999; 13 (1): 120-2
30. Bristow L, Bennett G. Biphasic effects of intra-accumbens histamine administration on spontaneous motor activity in the rat; a role for central histamine receptors. Br J Pharmacol 1988; 95 (4): 1292-304
31. Garbarg M, Tuong MD, Gros C, et al. Effects of histamine H3-receptor ligands on various biochemical indices of histaminergic neuron activity in rat brain. Eur J Pharmacol 1989; 164 (1): 1-11
32. McLeod RL, Aslanian R, del Prado M, et al. Sch 50971, an orally active histamine H3 receptor agonist, inhibits central neurogenic vascular inflammation and produces sedation in the guinea-pig. J Pharmacol Exp Ther 1998; 287 (1): 43-50
33. Lin JS, Sakai K, Vanni-Mercier G, et al. Involvement of histaminergic neurons in arousal mechanisms demonstrated with H3-receptor ligands in the cat. Brain Res 1990; 523 (2): 325-30
34. Carruthers S, Shoeman D, Hignite C, et al. Correlation between plasma diphenhydramine level and sedative and antihistamine effects. Clin Pharmacol Ther 1978; 23: 375-82
35. Wong L, Hendeles L, Weinberger M. Pharmacologic prophylaxis of allergic rhinitis: relative efficacy of hydroxyzine and chlorpheniramine. J Allergy Clin Immunol 1981; 67 (3): 223-8
36. Schweitzer PK, Muehlbach MJ, Walsh JK. Sleepiness and performance during three-day administration of cetirizine or diphenhydramine. J Allergy Clin Immunol 1994; 94 (4): 716-24
37. Spaeth J, Klimek L, Mosges R. Sedation in allergic rhinitis is caused by the condition and not by antihistamine treatment. Allergy 1996; 51 (12): 893-906
38. Roth T, Roehrs T, Koshorek G, et al. Sedative effects of antihistamines. J Allergy Clin Immunol 1987; 80 (1): 94-8
39. Simons FE, Fraser TG, Reggin JD, et al. Adverse central nervous system effects of older antihistamines in children. Pediatr Allergy Immunol 1996; 7 (1): 22-7
40. Marshall PS, Colon EA. Effects of allergy season on mood and cognitive function. Ann Allergy 1993; 71 (3): 251-8
41. Vuurman EF, van Veggel LM, Sanders RL, et al. Effects of semprex-D and diphenhydramine on learning in young adults with seasonal allergic rhinitis. Ann Allergy Asthma Immunol 1996; 76 (3): 247-52
42. Uden DL, Huska DR, Kellenberger TA, et al. Antihistamines: a study of pediatric usage and incidence of toxicity. Vet Hum Toxicol 1984; 26 (6): 469-72
43. Hestand HE, Teske DW. Diphenhydramine hydrochloride intoxication. J Pediatr 1977; 90 (6): 1017-8
44. Wyngaard JB, Seevers MH. The toxic effects of antihistaminic drugs. JAMA 1951; 145 (5): 277-82
45. Koppel C, Ibe K, Tenczer J. Clinical symptomatology of diphenhydramine overdose: an evaluation of 136 cases in 1982 to 1985. J Toxicol Clin Toxicol 1987; 25 (1-2): 53-70
46. Clark RF, Vance MV. Massive diphenhydramine poisoning resulting in a wide-complex tachycardia: successful treatment with sodium bicarbonate. Ann Emerg Med 1992; 21 (3): 318-21
47. Rinder CS, D'Amato SL, Rinder HM, et al. Survival in complicated diphenhydramine overdose. Crit Care Med 1988; 16 (11): 1161-2
48. Krenzelok EP, Anderson GM, Mirick M. Massive diphenhydramine overdose resulting in death. Ann Emerg Med 1982; 11 (4): 212-3
49. Winn RE, McDonnell KP. Fatality secondary to massive overdose of dimenhydrinate. Ann Emerg Med 1993; 22 (9): 1481-4
50. Simonser L. Top 200 drugs of 1992. Pharm Times 1993; 59: 29-44
51. Guill MF, Buckley RH, Rocha Jr W, et al. Multicenter, double-blind, placebo-controlled trial of terfenadine suspension in the treatment of fall-allergic rhinitis in children. J Allergy Clin Immunol 1986; 78 (1 Pt 1): 4-9
52. Moller C, Andlin-Sobocki P, Blychert LO. Pharmacokinetics of astemizole in children. Rhinol Suppl 1992; 13: 21-5
53. Mangalan S, Patel RB, Gandhi TP, et al. Detection and determination of free and plasma protein-bound astemizole by thin-layer chromatography: a useful technique for bioavailability studies. J Chromatogr 1991; 567 (2): 498-503
54. Slater JW, Zechnich AD, Haxby DG. Second-generation antihistamines: a comparative review. Drugs 1999; 57 (1): 31-47
55. McTavish D, Sorkin EM. Azelastine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential. Drugs 1989; 38 (5): 778-800
56. Watson WT, Simons KJ, Chen XY, et al. Cetirizine: a pharmacokinetic and pharmacodynamic evaluation in children with seasonal allergic rhinitis. J Allergy Clin Immunol 1989; 84 (4 Pt 1): 457-64

57. Desager JP, Dab I, Horsmans Y, et al. A pharmacokinetic evaluation of the second-generation H1-receptor antagonist cetirizine in very young children. Clin Pharmacol Ther 1993; 53 (4): 431-5
58. Spicak V, Dab I, Hulhoven R, et al. Pharmacokinetics and pharmacodynamics of cetirizine in infants and toddlers. Clin Pharmacol Ther 1997; 61 (3): 325-30
59. Horsmans Y, Desager JP, Hulhoven R, et al. Single-dose pharmacokinetics of cetirizine in patients with chronic liver disease. J Clin Pharmacol 1993; 33 (10): 929-32
60. Campoli-Richards DM, Buckley MM, Fitton A. Cetirizine: a review of its pharmacological properties and clinical potential in allergic rhinitis, pollen-induced asthma, and chronic urticaria. Drugs 1990; 40 (5): 762-81
61. Yamaguchi T, Hashizume T, Matsuda M, et al. Pharmacokinetics of the H1-receptor antagonist ebastine and its active metabolite carebastine in healthy subjects. Arzneimittel Forschung 1994; 44 (1): 59-64
62. Roberts DJ, Llenas J. Some observations on the cardiotoxic and drug interaction profiles of second generation antihistamines as measured in the guinea-pig. Arzneimittel Forschung 1996; 46 (8): 832-3
63. Simons FE, Watson WT, Simons KJ. Pharmacokinetics and pharmacodynamics of ebastine in children. J Pediatr 1993; 122 (4): 641-6
64. Simons FE, Bergman JN, Watson WT, et al. The clinical pharmacology of fexofenadine in children. J Allergy Clin Immunol 1996; 98 (6 Pt 1): 1062-4
65. Markham A, Wagstaff AJ. Fexofenadine. Drugs 1998; 55 (2): 269-74; discussion 275-6
66. Haria M, Fitton A, Peters DH. Loratadine: a reappraisal of its pharmacological properties and therapeutic use in allergic disorders. Drugs 1994; 48 (4): 617-37
67. Desager JP, Horsmans Y. Pharmacokinetic-pharmacodynamic relationships of H1-antihistamines. Clin Pharmacokinet 1995; 28 (5): 419-32
68. Vorperian VR, Zhou Z, Mohammad S, et al. Torsade de pointes with an antihistamine metabolite: potassium channel blockade with desmethylastemizole. J Am Coll Cardiol 1996; 28 (6): 1556-61
69. Handley D, Hong Y, Bakale R, et al. Norastemizole. Drug Future 1998; 23: 966-9
70. Paton DM, Webster DR. Clinical pharmacokinetics of H1-receptor antagonists (the antihistamines). Clin Pharmacokinet 1985; 10 (6): 477-97
71. Barlow JL, Beitman RE, Tsai TH. Terfenadine, safety and tolerance in controlled clinical trials. Arzneimittel Forschung 1982; 32 (9a): 1215-7
72. Klein GL, Littlejohn Tr, Lockhart EA, et al. Brompheniramine, terfenadine, and placebo in allergic rhinitis. Ann Allergy Asthma Immunol 1996; 77 (5): 365-70
73. Kemp JP, Falliers CJ, Fox RW, et al. A multicenter, open study of the non-sedating antihistamine, terfenadine (Seldane), in the maintenance therapy of seasonal allergic rhinitis. Ann Allergy 1988; 60 (4): 349-54
74. Buckley CEd, Klemawesch SJ, Lucas SK. Treatment of allergic rhinitis with a new selective H1 antihistamine: terfenadine. N Engl Reg Allergy Proc 1985; 6 (1): 63-70
75. Kemp JP, Buckley CE, Gershwin ME, et al. Multicenter, double-blind, placebo-controlled trial of terfenadine in seasonal allergic rhinitis and conjunctivitis. Ann Allergy 1985; 54 (6): 502-9
76. Lockey RF, Widlitz MD, Mitchell DQ, et al. Comparative study of cetirizine and terfenadine versus placebo in the symptomatic management of seasonal allergic rhinitis. Ann Allergy Asthma Immunol 1996; 76 (5): 448-54
77. Lockey RF, Findley S, Mitchell DQ, et al. Effects of cetirizine versus terfenadine in seasonal allergic rhinitis. Ann Allergy 1993; 70 (4): 311-5
78. Ten Eick AP, Nakamura H, Reed MD. Drug-drug interactions in pediatric psychopharmacology. Pediatr Clin North Amer 1998; 45 (5): 1233-64
79. Davies A, Harindra V, McEwan A, et al. Cardiotoxic effect with convulsions interfenadine overdose [letter]. BMJ 1989; 298: 325
80. Monahan B, Ferguson C, Killeavy E, et al. Torsade de pointes occurring in association with terfenadine use. JAMA 1990; 264: 2788-90
81. Pulmonary-Allergy Drugs Advisory Committee. Proceedings of the Pulmonary-Allergy Drugs Advisory Committee. Rockville (MD): Food and Drug Administration, Public Health Service, US Department of Health and Human Services, 1990
82. Marion Merrell Dow, Inc. Important drug warning [letter]. Cincinnati (OH): Marion Merrell Dow Inc. 1990 Aug 6
83. Woosley R, Darrow WR. Analysis of potential adverse drug reactions - a case of mistaken identity. Am J Cardiol 1994; 74 (2): 208-9
84. Woosley RL, Chen Y, Freiman JP, et al. Mechanism of the cardiotoxic actions of terfenadine. JAMA 1993; 269 (12): 1532-6
85. Salata JJ, Jurkiewicz NK, Wallace AA, et al. Cardiac electrophysiological actions of the histamine H1-receptor antagonists astemizole and terfenadine compared with chlorpheniramine and pyrilamine. Circ Res 1995; 76 (1): 110-9
86. Berul CI, Morad M. Regulation of potassium channels by nonsedating antihistamines. Circulation 1995; 91 (8): 2220-5
87. Follmer C, Colatsky T. Block of delay rectifier potassium current, Ik, by flecainide and E-4031 in cat ventricular myocytes. Circulation 1990; 82: 289-93
88. Ducic I, Ko CM, Shuba Y, et al. Comparative effects of loratadine and terfenadine on cardiac K+ channels. J Cardiovasc Pharmacol 1997; 30 (1): 42-54
89. Roy M, Dumaine R, Brown AM. HERG, a primary human ventricular target of the nonsedating antihistamine terfenadine. Circulation 1996; 94 (4): 817-23
90. Honig PK, Wortham DC, Zamani K, et al. Terfenadine-ketoconazole interaction. Pharmacokinetic and electrocardiographic consequences. JAMA 1993; 269 (12): 1513-8
91. Moss AJ, Morganroth J. Cardiac effects of ebastine and other antihistamines in humans. Drug Saf 1999; 21 Suppl. 1: 69-80
92. Chen Y, Woosley R. Electrophysiologic actions of astemizole [abstract]. Clin Pharmacol Ther 1994: 146
93. Woosley RL. Cardiac actions of antihistamines. Annu Rev Pharmacol Toxicol 1996; 36: 233-52
94. Carlison M, editor. New drug application pipeline. 17th ed. Chevychase (MD): SDC Report, Inc., 1998
95. Zhou Z, Vorperian VR, Gong Q, et al. Block of HERG potassium channels by the antihistamine astemizole and its metabolites desmethylastemizole and norastemizole. J Cardiovasc Electrophysiol 1999; 10 (6): 836-43
96. Kothari SS, Sharma S, Wasir HS. Terfenadine overdose induced polymorphous ventricular tachycardia. Indian Pediatr 1995; 32 (10): 1107-08
97. Bishop R, Gaudry P. Prolonged Q-T interval following astemizole overdose. Arch Emerg Med 1989; 6: 63-5

98. Clark A, Love H. Astemizole-induced ventricular arrhythmias: an unexpected cause of convulsions. Int J Cardiol 1991; 33: 165-67
99. Craft TM. Torsade de pointes after astemizole overdose. BMJ (Clin Res Ed) 1986; 292 (6521): 660
100. Hoppu K, Tikanoja T, Tapanainen P, et al. Accidental astemizole overdose in young children. Lancet 1991; 338: 538-40
101. Tobin JR, Doyle TP, Ackerman AD, et al. Astemizole-induced cardiac conduction disturbances in a child. JAMA 1991; 266: 2737-40
102. Wiley JF, Gelber ML, Henretig FM, et al. Cardiotoxic effects of astemizole overdose in children. J Pediatr 1992; 120 (5): 799-802
103. Hasan RA, Zureikat GY, Nolan BM. Torsade de Pointes associated with astemizole overdose treated with magnesium sulfate. Pediatr Emerg Care 1993; 9: 23-5
104. Broadhurst P, Nathan AW. Cardiac arrest in a young woman with the long QT syndrome and concomitant astemizole ingestion. Br Heart J 1993; 70: 469-70
105. Rao KA, Adlakha A, Verma-Ansil B, et al. Torsades de pointes ventricular tachycardia associated with overdose of astemizole. Mayo Clin Proc 1994; 69 (6): 589-93
106. Ikeda S, Oka H, Matunaga K, et al. Astemizole-induced torsades de pointes in a patient with vasospastic angina. Jpn Circ J 1998; 62 (3): 225-7
107. Tsai WC, Tsai LM, Chen JH. Combined use of astemizole and ketoconazole resulting in torsade de pointes. J Formos Med Assoc 1997; 96 (2): 144-6
108. June RA, Nasr I. Torsades de pointes with terfenadine ingestion. Am J Emerg Med 1997; 15 (5): 542-3
109. Hilbert J, Radwanski E, Weglein R, et al. Pharmacokinetics and dose proportionality of loratadine. J Clin Pharmacol 1987; 27 (9): 694-8
110. Matzke GR, Halstenson CE, Opsahl JA, et al. Pharmacokinetics of loratadine in patients with renal insufficiency. J Clin Pharmacol 1990; 30 (4): 364-71
111. Yumibe N, Huie K, Chen KJ, et al. Identification of human liver cytochrome P450s involved in the microsomal metabolism of the antihistaminic drug loratadine. Int Arch Allergy Immunol 1995; 107 (1-3): 420
112. Brannan MD, Reidenberg P, Radwanski E, et al. Loratadine administered concomitantly with erythromycin: pharmacokinetic and electrocardiographic evaluations. Clin Pharmacol Ther 1995; 58 (3): 269-78
113. Siegel S, Ellis E, Kemp J, et al. Efficacy and safety of loratadine in the treatment of allergic rhinitis in children [abstract A-2]. Allergy 1988; 43 Suppl. 7: 5
114. Lutsky BN, Schuller JL, Cerio R, et al. Comparative study of the efficacy and safety of loratadine syrup and terfenadine suspension in the treatment of chronic allergic skin diseases in a pediatric population. Arzneimittel Forschung 1993; 43 (11): 1196-9
115. Lutsky BN, Klose P, Melon J, et al. A comparative study of the efficacy and safety of loratadine syrup and terfenadine suspension in the treatment of 3- to 6-year-old children with seasonal allergic rhinitis. Clin Ther 1993; 15 (5): 855-65
116. Boner AL, Richelli C, Castellani C, et al. Comparison of the effects of loratadine and astemizole in the treatment of children with seasonal allergic rhinoconjunctivitis. Allergy 1992; 47 (2 Pt 1): 98-102
117. Del Carpio J, Kabbash L, Turenne Y, et al. Efficacy and safety of loratadine (10 mg once daily), terfenadine (60 mg twice daily), and placebo in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol 1989; 84 (5 Pt 1): 741-6
118. VanCauwenberge P. New data on the safety of loratadine. Drug Invest 1992; 4: 283-91
119. Hey JA, del Prado M, Egan RW, et al. Loratadine produces antihistamine activity without adverse CNS, ECG or cardiovascular effects in guinea-pigs. Comparative studies with terfenadine and sedating antihistamines. Int Arch Allergy Immunol 1995; 107 (1-3): 418-9
120. Sanguinetti N, Jiang C, Durran M, et al. A mechanistic link between an inherited and an acquired cardiac arrhythmia: HERG encodes the Ikr potassium channel. Cell 1995; 81: 1-20
121. Lacerda AE, Roy ML, Lewis EW, et al. Interactions of the nonsedating antihistamine loratadine with a Kv1.5- type potassium channel cloned from human heart [published erratum appears in Mol Pharmacol 1997 Oct; 52 (4): 754]. Mol Pharmacol 1997; 52 (2): 314-22
122. Delpon E, Valenzuela C, Gay P, et al. Block of human cardiac Kv1.5 channels by loratadine: voltage-, time- and use-dependent block at concentrations above therapeutic levels. Cardiovasc Res 1997; 35 (2): 341-50
123. Caballero R, Delpon E, Valenzuela C, et al. Effect of descarboethoxyloratadine, the major metabolite of loratadine, on the human cardiac potassium channel Kv1.5. Br J Pharmacol 1997; 122 (5): 796-8
124. Loratadine product information. 2nd rev. Kenilworth (NJ): Schering, 1998
125. Good AP, Rockwood R, Schad P. Loratadine and ventricular tachycardia. Am J Cardiol 1994; 74 (2): 207
126. Hashizume T, Mise M, Terauchi Y, et al. N-Dealkylation and hydroxylation of ebastine by human liver cytochrome P450. Drug Metab Dispos 1998; 26 (6): 566-71
127. Moss AJ, Chaikin P, Garcia JD, et al. A review of the cardiac systemic side effects of antihistamines: ebastine. Clin Exp Allergy 1999; 26 (Suppl. 3): 200-5
128. Imai T, Taketani M, Suzu T, et al. In vitro identification of the human cytochrome P-450 enzymes involved in the N-demethylation of azelastine. Drug Metab Dispos 1999; 27 (8): 942-6
129. Nakajima M, Nakamura S, Tokudome S, et al. Azelastine N-demethylation by cytochrome P-450 (CYP)3A4, CYP2D6, and CYP1A2 in human liver microsomes: evaluation of approach to predict the contribution of multiple CYPs. Drug Metab Dispos 1999; 27 (12): 1381-91
130. Anonymous. An evaluation of the efficacy and safety of azelastine in patients with chronic asthma. Azelastine-Asthma Study Group. J Allergy Clin Immunol 1996; 97 (6): 1218-24
131. Tinkelman DG, Bucholtz GA, Kemp JP, et al. Evaluation of the safety and efficacy of multiple doses of azelastine to adult patients with bronchial asthma over time. Am Rev Respir Dis 1990; 141 (3): 569-74
132. Pichat P, Angel I, Arbilla S. Anti-inflammatory properties of mizolastine after oral administration on arachidonic acid-induced cutaneous reaction in the rat. Arzneimittel Forschung 1998; 48 (2): 173-8
133. Gillen M, Pentikis H, Rhodes G, et al. Pharmacokinetic and cardiac safety studies of ebastine and loratadine administered with ketoconazole [abstract]. J Clin Pharmacol 1998; 38: 867
134. Gillen M, Pentikis H, Rhodes G, et al. Pharmacokinetic and pharmacodynamic interaction of ebastine and erythromycin [abstract]. J Clin Pharmacol 1998; 38: 878

135. Moss AJ, Morganroth J. Cardiac effects of ebastine and other antihistamines in humans. Drug Saf 1999; 21: 69-80
136. Sale M, Lyness W, Perhach J, et al. Lack of effect of coadministration of erythromycin with azelastine on pharmacokinetic or ECG parameters. Ann Allergy Asthma Imunol 1996; 76: 91
137. Delauche-Cavallier MC, Chaufour S, Guerault E, et al. QT interval monitoring during clinical studies with mizolastine, a new H1 antihistamine. Clin Exp Allergy 1999; 29 Suppl. 3: 206-11
138. Wiseman LR, Faulds D. Ebastine. a review of its pharmacological properties and clinical efficacy in the treatment of allergic disorders. Drugs 1996; 51 (2): 260-77
139. Riethmuller-Winzen H, Peter G, Buker KM, et al. Tolerability, pharmacokinetics and dose linearity of azelastine hydrochloride in healthy subjects. Arzneimittel Forschung 1994; 44 (10): 1136-40
140. LaForce C, Dockhorn RJ, Prenner BM, et al. Safety and efficacy of azelastine nasal spray (Astelin NS) for seasonal allergic rhinitis: a 4-week comparative multicenter trial. Ann Allergy Asthma Immunol 1996; 76 (2): 181-8
141. Hey JA, del Prado M, Sherwood J, et al. Comparative analysis of the cardiotoxicity proclivities of second generation antihistamines in an experimental model predictive of adverse clinical ECG effects. Arzneimittel Forschung 1996; 46 (2): 153-8
142. Ohtani H, Sato H, Iga T, et al. Pharmacokinetic-pharmacodynamic analysis of the arrhythmogenic potency of a novel antiallergic agent, ebastine, in rats. Biopharm Drug Dispos 1999; 20 (2): 101-6
143. Ko CM, Ducic I, Fan J, et al. Suppression of mammalian K+ channel family by ebastine. J Pharmacol Exp Ther 1997; 281 (1): 233-44
144. Hurst M, Spencer CM. Ebastine: an update of its use in allergic disorders. Drugs 2000; 59 (4): 981-1006
145. Data on file, Wallace Laboratories, Cranbury, 2000
146. Weiler JM, Donnelly A, Campbell BH, et al. Multicenter, double-blind, multiple-dose, parallel-groups efficacy and safety trial of azelastine, chlorpheniramine, and placebo in the treatment of spring allergic rhinitis. J Allergy Clin Immunol 1988; 82 (5 Pt 1): 801-11
147. Charpin D, Godard P, Garay RP, et al. A multicenter clinical study of the efficacy and tolerability of azelastine nasal spray in the treatment of seasonal allergic rhinitis: a comparison with oral cetirizine. Eur Arch Otorhinolaryngol 1995; 252 (8): 455-8
148. Gambardella R. A comparison of the efficacy of azelastine nasal spray and loratidine tablets in the treatment of seasonal allergic rhinitis. J Int Med Res 1993; 21 (5): 268-75
149. Morganroth J, Lyness WH, Perhach JL, et al. Lack of effect of azelastine and ketoconazole coadministration on electrocardiographic parameters in healthy volunteers. J Clin Pharmacol 1997; 37 (11): 1065-72
150. Rosenzweig P, Patat A. Lack of behavioural toxicity of mizolastine: a review of the clinical pharmacology studies. Clin Exp Allergy 1999; 29 Suppl. 3: 156-62
151. Allegra product information. 2nd rev. New York (NY): Hoechst-Marion Roussel, 2000
152. Pagliara A, Testa B, Carrupt PA, et al. Molecular properties and pharmacokinetic behavior of cetirizine, a zwitterionic H1-receptor antagonist. J Med Chem 1998; 41 (6): 853-63
153. Wood SG, John BA, Chasseaud LF, et al. The metabolism and pharmacokinetics of 14C-cetirizine in humans. Ann Allergy 1987; 59 (6 Pt 2): 31-4
154. Pellegrin P, Jacqmin P, Van Bel P, et al. Mechanism of the renal clearance of cetirizine. Abstract 247. Euro J Drug Metab Pharmacokinet 1990; 15 Suppl. 2: 31
155. Cetirizine (Zylert) product information. 2nd rev. New York (NY): Pfizer, 2000
156. Taglialatela M, Pannaccione A, Castaldo P, et al. Molecular basis for the lack of HERG K+ channel block-related cardiotoxicity by the H1 receptor blocker cetirizine compared with other second-generation antihistamines. Mol Pharmacol 1998; 54 (1): 113-21
157. Carmeliet E. Effects of cetirizine on the delayed K+ currents in cardiac cells: comparison with terfenadine. Br J Pharmacol 1998; 124 (4): 663-8
158. Winder J, Noonan M, Lumry W, et al. Absence of QTc prolongation with cetirizine in children aged 6 to 11 years. Pediatr Asthma Allergy Immunol 1996; 10: 181-90
159. Sale ME, Barbey JT, Woosley RL, et al. The electrocardiographic effects of cetirizine in normal subjects. Clinical Pharmacol Ther 1994; 56: 295-301
160. Russell T, Stoltz M, Weir S. Pharmacokinetics, pharmacodynamics, and tolerance of single- and multiple-dose fexofenadine hydrochloride in healthy male volunteers. Clin Pharmacol Ther 1998; 64 (6): 612-21
161. Ridout SM, Tariq SM. Cetirizine overdose in a young child. J Allergy Clin Immunol 1997; 99 6 Pt 1: 860-1
162. Hansen JJ, Feilberg Jorgensen NH. Accidental cetirizine poisoning in a four-year-old boy. Ugeskr Laeger 1998; 160 (41): 5946-7
163. Giraud T. QT lengthening and arrhythmias associated with fexofenadine. Lancet 1999; 353 (9169): 2072-3
164. Pinto YM, van Gelder IC, Heeringa M, et al. QT lengthening and life-threatening arrhythmias associated with fexofenadine [letter]. Lancet 1999; 353: 980
165. Pinto YM, van Gelder IC, Heeringa M, et al. QT lengthening and arrhythmias associated with fexofenadine [letter]. Lancet 1999; 353; 2072-3
166. Witek Jr TJ, Canestrari DA, Miller RD, et al. Characterization of daytime sleepiness and psychomotor performance following H1 receptor antagonists. Ann Allergy Asthma Immunol 1995; 74 (5): 419-26
167. Tharion WJ, McMenemy DJ, Rauch TM. Antihistamine effects on the central nervous system, cognitive performance and subjective states. Neuropsychobiology 1994; 29 (2): 97-104
168. Kay GG, Berman B, Mockoviak SH, et al. Initial and steady-state effects of diphenhydramine and loratadine on sedation, cognition, mood, and psychomotor performance. Arch Intern Med 1997; 157 (20): 2350-6
169. Seidel WF, Cohen S, Bliwise NG, et al. Cetirizine effects on objective measures of daytime sleepiness and performance. Ann Allergy 1987; 59 (6 Pt 2): 58-62
170. Gengo FM, Gabos C. Antihistamines, drowsiness, and psychomotor impairment: central nervous system effect of cetirizine. Ann Allergy 1987; 59 (6 Pt 2): 53-7
171. Gengo FM, Dabronzo J, Yurchak A, et al. The relative antihistaminic and psychomotor effects of hydroxyzine and cetirizine. Clin Pharmacol Thera 1987; 42 (3): 265-72
172. Backhouse CI, Renton R, Fidler C, et al. Multicentre, double-blind comparison of terfenadine and cetirizine in patients with seasonal allergic rhinitis. Br J Clin Pract 1990; 44 (3): 88-91
173. Spencer CM, Faulds D, Peters DH. Cetirizine: a reappraisal of its pharmacological properties and therapeutic use in selected allergic disorders. Drugs 1993; 46 (6): 1055-80

174. Simons FE. H1-receptor antagonists. Comparative tolerability and safety. Drug Saf 1994; 10 (5): 350-80
175. Adelsberg BR. Sedation and performance issues in the treatment of allergic conditions. Arch Intern Med 1997; 157 (5): 494-500
176. Moskowitz H, Burns M. Effects of terfenadine, diphenhydramine, and placebo on skills performance. Cutis 1988; 42 (4A): 14-8
177. Nicholson AN, Stone BM. Performance studies with the H1-histamine receptor antagonists, astemizole and terfenadine. Br J Clin Pharmacol 1982; 14: 199-202
178. Vermeeren A, O'Hanlon JF. Fexofenadine's effects, alone and with alcohol, on actual driving and psychomotor performance. J Allergy Clin Immunol 1998; 101 (3): 306-11
179. O'Hanlon JF, Ramaekers JG. Antihistamine effects on actual driving performance in a standard test: a summary of Dutch experience, 1989-94. Allergy 1995; 50 (3): 234-42
180. Napolitano C, Priori S, Schwartz P. Torsade de pointes: mechanisms and management. Drugs 1994; 47: 51-65

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