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New Insights into the Second Generation Antihistamines

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Abstract

Second generation antihistamines are recognised as being highly effective treatments for allergy-based disease and are among the most frequently prescribed and safest drugs in the world. However, consideration of the therapeutic

index or the benefit/risk ratio of the H_1 receptor antagonists is of paramount importance when prescribing this class of compounds as they are used to treat non-life threatening conditions. There are many second generation antihistamines available and at first examination these appear to be comparable in terms of safety and efficacy. However, the newer antihistamines in fact represent a hererogeneous group of compounds, having markedly differing chemical structures, adverse effects, half-life, tissue distribution and metabolism, spectrum of antihistaminic properties, and varying degrees of anti-inflammatory effects. With regard to the latter, there is growing awareness that some of these compounds might represent useful adjunct medications in asthma therapy. In terms of safety issues, the current second generation grouping includes compounds with proven cardiotoxic effects and others with the potential for adverse drug interactions. Moreover, some of the second generation H_1 antagonists have given cause for concern regarding their potential to cause a degree of somnolence in some individuals. It can be argued, therefore, that the present second generation grouping is too large and indistinct since this was based primarily on the concept of separating the first generation sedating compounds from nonsedating H_1 antagonists. Although it is too early to talk about a third generation grouping of antihistamines, future membership of such a classification could be based on a low volume of distribution coupled with a lack of sedating effects, drug interactions and cardiotoxicity.

Over the past 30 years the prevalence of asthma, rhinitis and dermatitis has increased remarkably in many countries,[1] and this in turn has led to a greater awareness of the social and economic costs of allergic diseases. Therapeutic intervention in allergy has often focused on blocking the effects of histamine release from mast cells and basophils, a major contributor to the allergic response. The emphasis of early research concentrated on antagonising the effects of histamine and led to the development of several potent antihistamines for the treatment of certain symptoms of allergic disease. However, histamine also functions as a neurotransmitter, being particularly important in maintaining a state of arousal or awareness within the CNS.[2]

First generation H_1 receptor antagonists have or show a marked tendency to cross the blood-brain barrier and their consequent well documented sedative and anticholinergic effects, together with a short half-life, greatly limited their use in the treatment of allergic symptoms. The second generation H_1 receptor antagonists have been developed over the past 15 years and have major advantages over the earlier drugs, most notably their lack of significant CNS and anticholinergic adverse effects. Therefore, they are considered to be a major pharmacological advance when compared with their predecessors and have proved to be important therapeutic tools in the treatment of atopic disease.[3,4]

To date, the classification of antihistamines as first or second generation drugs has been made on the basis of H_1 receptor versus muscarinic selectivity, combined with a much reduced tendency to cause sedation. The currently available second generation antihistamines include acrivastine, astemizole, azelastine, cetirizine, ebastine, epinastine, fexofenadine, levocabastine, loratadine, mizolastine and terfenadine (the last having recently been withdrawn from use). Both ketotifen and oxatomide can interfere with serotoninergic and cholinergic neurotransmission and are therefore considered to be intermediate between the first and second generation;[5] in addition to these compounds there are several new drugs undergoing clinical trials.

Thus, there are many second generation antihistamines available, and at first glance, there appears to be little to choose between them in terms of safety and efficacy. However, with the passage of

time it has become apparent that the newer antihistamines in fact represent a heterogeneous group of compounds, having markedly differing chemical structures,[6] with variations in therapeutic profiles, adverse effects, half-life, tissue distribution, metabolism, and varying degrees of anti-allergic effects. There has also been a great deal of concern regarding the possible cardiotoxic effects of some of the newer medications.[7] On this basis, it could be argued that the current grouping of second generation drugs is too large and that we need to reconsider and perhaps redefine what is meant by a true second generation antihistamine. The aim of the present paper is to evaluate existing information concerning the pharmacological properties of the second generation antihistamines currently available in an attempt to elucidate whether we are in a position to define a new third generation grouping.

1. Pharmacokinetics

With a few exceptions, antihistamines are rapidly and completely absorbed following oral administration; peak plasma concentrations are reached after 1 to 4 hours and, following recommended doses, are highly variable because of differences in metabolism and tissue distribution. Most of the second generation antihistamines (e.g. terfenadine, ebastine, astemizole and loratadine) undergo an extensive first-pass metabolism to pharmacologically-active metabolites; as a common feature, the reaction is primarily supported by cytochrome P450 (CYP) belonging to the CYP3A4 subfamily. Under normal circumstances this extensive metabolism leads to low or undetectable plasma concentrations of the parent drug. However, circumstances exist where metabolism of the parent compound can be compromised, e.g. in cases of liver insufficiency or of overdose. Although not genetically polymorphic, CYP3A4 demonstrates wide interindividual variability,[8] and it remains to be determined whether and to what extent this variability influences the safety and the therapeutic activity of antihistamines that act as prodrugs.

There are some second generation antihistamines which are not metabolised via CYP3A4. Although a substrate of CYP3A4, mizolastine is primarily (65%) metabolised *in vivo* by glucuronidation enzymes.[9] Of interest, the zwitterionic antihistamines cetirizine, acrivastine, carebastine, fexofenadine and epinastine show negligible, if any, metabolism.[10-12] Although less well documented, some second generation antihistamines have the potential to produce interactions through induction[13] or inhibition[14] of CYP activities, although the clinical significance of these findings remains to be determined. Interestingly, a number of *in vitro* studies suggest that terfenadine, azelastine and ebastine can reverse multidrug resistance by inhibiting an energy-dependent drug efflux pump, the P-glycoprotein (Pgp), whereas the more hydrophilic antihistamines cetirizine, fexofenadine and acrivastine are devoid of such inhibitory effects.[15-17] Besides cancer cells, Pgp is also found in the blood-brain barrier and in normal tissues such as the intestinal wall and proximal renal tubules. It is now recognised as an important factor in drug distribution and excretion and, not surprisingly, is the source of some important pharmacokinetic interactions.[18] To date, no studies have evaluated whether antihistamines can produce drug-drug interactions through inhibition of Pgp, although the terfenadine lesson illustrates how interactions with metabolising enzymes may have serious consequences. All the documented interactions which have been encountered with antihistamines relate to their ability to interact with CYP3A4 inhibitors. However, physicians must remain alert to other potential interaction mechanisms.

1.1 Drug Interactions

Among the currently available second generation antihistamines only acrivastine, cetirizine and fexofenadine are excreted with negligible liver metabolism.[10-12] The problem of interactions between second generation antihistamines and other coadministered drugs is a cause for concern. Many drugs can affect liver CYP enzyme function with consequent elevations in the plasma concentrations of unmetabolised parent compounds of those antihistamines which rely on extensive biotransforma-

tion. Coadministration of substances such as antifungals, macrolides and grapefruit juice can inhibit the function of the CYP3A4 enzyme system leading to accumulation of the unchanged drug. Examples of drug interactions encountered with antihistamines are given in table I. These potential interactions represent a major safety concern since it has been reported that accumulation of unchanged terfenadine and astemizole may affect cardiac repolarisation mainly through prolongation of the QT interval which, in some cases, can trigger serious ventricular arrhythmias (see section 2.3 on safety). Therefore, a number of studies have examined the effects of coadministration of antihistamines with other drugs.[26] For example, when cetirizine was administered concomitantly with CYP3A4 inhibitors ketoconazole,[27] erythromycin[28] or azithromycin,[29] no electrocardiographic change could be detected. The reported lack of significant change in cetirizine plasma or serum concentrations confirms no significant drug interactions or hepatic metabolism. Although ketoconazole inhibits the metabolism of loratadine[30] and there has been one published case of ventricular tachycardia with prolonged QT interval after loratidine treatment and coadministration of quinidine in a patient with ischaemic coronary disease,[31] in a clinical study, loratidine had no effect on the QTc interval despite an increased plasma concentration as a result of concomitant erythromycin treatment.[32]

Table I. Common interactions of histamine H_1 receptor antagonists with concomitantly-administered medications

Antihistamine	Interacting drug	Reference
Astemizole	Erythromycin	19
	Ketoconazole	19
Terfenadine	Ketoconazole	20
	Erythromycin	21
	Clarithromycin	21
	Azithromycin	21
Ebastine	Erythromycin	22
	Ketoconazole	23
Loratadine	Erythromycin	24
	Ketoconazole	24, 25
	Cimetidine	24

1.2 Physicochemistry and Tissue Distribution

1.2.1 H_1 Receptors

The first generation antihistamines have a relatively high liposolubility and are thought to cross the blood-brain barrier by a process of passive transport to interact with the H_1 receptors of the brain. These are numerous and, in humans, constitute about 40% of the total amount of H_1 receptors.[33] In an ideal world H_1 receptor antagonists would not cross the blood-brain barrier; however, this situation is difficult to achieve in practice, although it has been shown that brain transfer can be drastically limited.[34] H_1 receptors have a wide cellular distribution being found on smooth muscle cells, endothelial cells, mast cells, basophils and eosinophils; antihistamines exert their effects by competing with histamine for occupancy of these receptors.[35] In the 1980s it was established that the sedation induced by antihistamines was a consequence of their blockade of central H_1 receptors. Evidence for this was provided by a mouse model in which the sedative properties of antagonists significantly correlated with occupancy of the H_1 receptor.[36] In humans, administration of enantiomers of chlorphenamine and dimetindene caused sedation limited to the enantiomer with higher H_1 receptor affinity.[37]

It is possible that the reduced ability of the second generation H_1 receptor antagonists to cause sedation is related to the previously noted 'existence of differences' between CNS and peripheral H_1 receptors.[5] This idea is supported by studies which demonstrated that mequitazine[38] and loratadine[39] have a somewhat lower affinity for CNS H_1 receptors compared with peripheral H_1 receptors. However, a comprehensive study which examined both first and second generation antihistamines found no differences in their affinity for H_1 receptors obtained from either lung or cerebellum tissue.[40] Furthermore, work by Yamashita and colleagues[41] which utilised Northern blot analysis of mRNA for H_1 receptors cloned from bovine adrenal medulla failed to demonstrate any difference between CNS

and lung receptors. Therefore, it is unlikely that the reduced ability of the second generation antihistamines to cause sedation is a consequence of differences between CNS and peripheral H_1 receptors.

1.2.2 Lipophilicity

In general terms, and in the absence of active transport mechanisms, it has been observed that those compounds with an appropriate degree of lipophilicity enter the CNS while highly hydrophilic compounds do not;[42] in addition, compounds with a very high degree of lipophilicity do not pass the blood-brain barrier. Lipophilicity can be expressed as log P, indicating the partition of a given compound over an organic solvent and water. Thus, log $P_{oct/water}$ is defined as the logarithm of the ratio of the concentrations of a compound in l-octanol and water at equilibrium and at 25°C. A high log P denotes a high level of lipophilicity. The relationship between the central effect of a compound and its log P is often not linear but parabolic. The log P value associated with optimal penetration of the blood-brain barrier has in several cases been found to have a value of around 2.[43] The issue is further complicated when, in addition to its lipophilicity, the influence of the ionisation of a compound is taken into account. In this situation the ratio between the concentration of the neutral and protonated species of a compound depends on its pK_a. Obviously, the apparent log P depends on the pH of the solution and is indicated as log D. Assuming that the only the neutral species is involved in partition over the organic solvent and water, log D at a certain pH can be calculated from: $\log D_{pH} = \log P - \log(1 + 10^{pKa-pH})$. When the log Ds of several antihistamines are examined at neutral pH ($\log D_{7.4} = \log P - \log (1+ 10^{(pKa-7.4)})$ notable differences can be observed (table II). For example, the sedating antihistamine azatadine has a Log $D_{7.4}$ of 1.68 whereas its analogue loratadine has a Log $D_{7.4}$ of 4.4. In contrast cetirizine has a Log $D_{7.4}$ of 1.04 whereas the sedating first generation parent compound hydroxyzine has a higher Log $D_{7.4}$ of 2.87.[44]

Another useful parameter is Δlog P which is defined as the difference of log Ps measured in l-octanol/water and cyclohexane/water, i.e. $\Delta\log P = \log P_{oct\text{-}water} - \log P_{cycl/water}$. Thus, a high Δlog P denotes a compound which dissolves more readily in octanol than cyclohexane which is dependent on the hydrogen bonding capacity of octanol versus the neutral behaviour of cyclohexane. A high Δlog P is therefore associated with a high hydrogen bonding capacity of a compound which in turn may result in enhanced binding to serum proteins and thus restrict penetration of the blood-brain barrier.[45] It can be appreciated from the data presented in table II that Δlog P alone is not a reliable

Table II. Lipophilicity parameters of selected antihistamines.[44] See figure 1 for application

Number for reference to fig. 1	Drug	log P_{oct}	log P_{dod}	$\Delta \log_{oct\text{-}alk}$	log $D_{oct, 7.4}$
1.	Imipramine	4.44	3.98	0.46	2.33
2.	Chlorpheniramine	3.17	2.09	1.08	1.40
3.	Diphenhydramine	3.17	2.56	0.61	1.58
4.	Mepyramine	2.96	2.00	0.96	1.43
5.	Azatadine	3.59	1.82	1.77	1.68
6.	Hydroxyzine	3.05	1.09	1.96	2.87
7.	Dimetindene	2.70	1.65	1.05	1.61
8.	Loratadine	4.40	2.4	2.00	4.40
9.	Cetirizine	4.48	0.61	3.87	1.04
10.	Temelastine	3.19	1.28	1.91	3.19
11.	Astemizole	3.56	0.95	2.61	3.48
12.	Epinastine	3.51	1.76	1.75	-0.75
13.	Terfenadine	5.69	2.63	3.06	4.46

alk = alkaline pH; **dod** = dodecane; **log $D_{oct, 7.4}$** = log D in octanol at pH 7.4; **oct** = n-octanol.

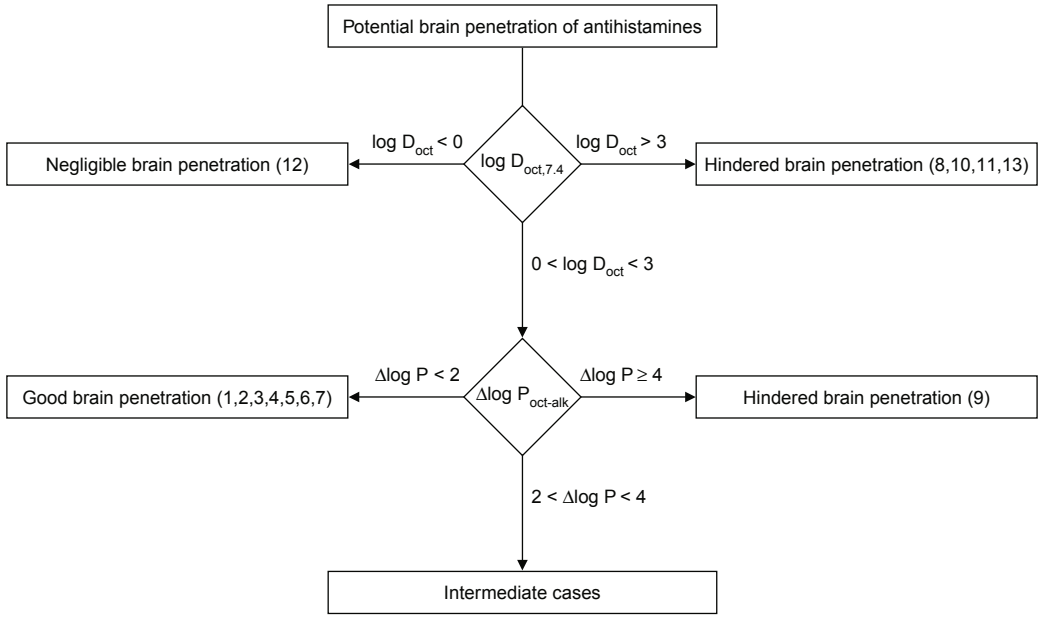

Fig. 1. Hypothetical model for the brain penetration capacity of antihistamines. See section 1.2.2 for explanation and definition of lipophilicity parameters. Numbers in brackets refer to the antihistamines listed in table II with their associated lipophilicity parameters.

predictor of the ability of the first and second generation antihistamines to penetrate the CNS. However, when the data in table II is used in conjunction with the hypothetical model for the brain penetration capacity of antihistamines shown in figure 1 and applied to those compounds with an intermediate log D_{oct}, the Δlog P concept becomes more attractive. Whereas a Δlog P value of less than 2 denotes good brain penetration, values in the region of 4 indicate a poor capacity to reach the CNS. Although the precise significance of Δlog P remains to be elucidated, use of table II in combination with figure 1 may be helpful in predicting the ability of a given antihistamine to penetrate the CNS. Other factors which might be important include the binding of antihistamines by serum proteins such as albumin and also the volume of distribution (V_d) of this class of compounds.

1.2.3 Volume of Distribution

In pharmacokinetic terms it is desirable for any drug to have the lowest V_d compatible with the therapeutic goal of interaction with the target receptors at effective concentrations while avoiding organs where the drug is ineffective or potentially toxic. A low V_d can be defined as being less than the volume of exchangeable water in the body which is freely and quickly exchanged between extracellular fluids and cytosol; this concept is illustrated in figure 2. Evaluation with phenazone (antipyrine) has shown the volume of exchangeable water to be 0.6 L/kg.[47] A low V_d may represent a distinct advantage for an H_1 receptor antagonist as it would optimise the body distribution to the targeted receptors and minimise the potential to cross the blood-brain barrier.

Table III shows the pharmacokinetic parameters in humans of a number of the currently available second generation antihistamines. Among these, cetirizine has the lowest V_d followed by acrivastine suggesting that their distribution is poor in tissues and organs. In contrast, the majority of H_1 receptor antagonists have large apparent volumes of distribution and total body clearance.[46,48] It is unlikely that an extensive tissue distribution would be re-

quired for the mode of action of H_1 receptor antagonists and it may be of interest to look for a correlation between the frequency of adverse effects and corresponding V_d as these might be linked to the relative accumulation of this class of drugs. The association constant of the binding of an antihistamine to human serum albumin (HSA) is insufficient in itself to explain its low V_d; this may be related to other mechanisms including the ionisation of the molecule, its low lipophilicity and its H_1 receptor specificity.[49] The advantages conferred on a drug by having a low V_d include minimal risk of dose-dependent toxicity, minimal inter-individual variation in the therapeutic effect, a reduction in unwanted drug-drug interactions and no accumulation in the heart or liver.

1.2.4 Zwitterionic Antihistamines

Classical H_1 receptor antagonists are lipophilic drugs with a single strongly basic centre, which at physiological pH exist mostly as lipophilic cations. However, a number of antihistamines exist as zwitterionic forms and these include acrivastine, cetirizine, levocabastine and fexofenadine (table III). The effect that this property confers on the pharmacokinetic behaviour of an antihistamine has been most extensively investigated for cetirizine.[50] This recent study investigated the ionisation and lipophilicity behaviour of cetirizine and demonstrated that it exists almost exclusively as a zwitterion in the pH region 3.5 to 7.5 in which its octanol/water lipophilicity was found to be constant and low compared with other cationic antihistamines (log D = log P^z = 1.5), whereas its hydrogen bonding capacity is relatively large ($\Delta\log P^z \geq$ 3.1). Conformational, electronic and lipophilicity potential calculations revealed that zwitterionic cetirizine experiences partial intramolecular charge neutralisation in folded conformers of lower polarity factors. These observations may contribute further to our understanding of the pharmacokinetic behaviour of cetirizine.

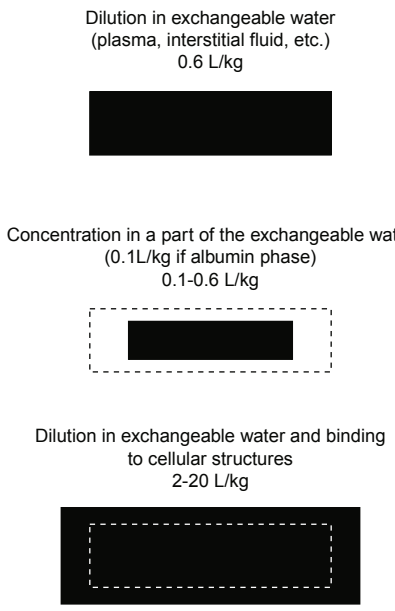

Fig. 2. Schematic representation of the possible volumes of distribution of a drug.[46]

2. Safety

The currently available second generation antihistamines are recognised as being highly effective treatments for allergy-based disease, and are among the most frequently prescribed and safest drugs in the world. However, consideration of the therapeutic index or the benefit/risk ratio of the H_1 receptor antagonists is of paramount importance when prescribing this class of compounds as they are used to treat non-life-threatening conditions. Furthermore, antihistamines are frequently used by individuals who wish or have to remain alert and active, and who might also be taking other medications. Consequently, progress with this class of drugs should involve not only increased efficacy but also improvements in their safety and specificity.

2.1 Sedation

For many people, sedation remains the primary concern when considering the adverse effects of the newer antihistamines, particularly since these drugs are given to patients with chronic disorders with treatment periods which often extend over several months. This raises the question of how

Table III. Pharmacokinetic parameters of some second generation antihistamines in humans[46,47]

Drug	Terminal half-life (hours)	Bound in plasma (%)	Volume of distribution (V_d)
Astemizole	26	96	48
Azelastine	25	NA	14.5
Ebastine	10 - 12	NA	NA
Loratadine	12 ± 4	97	120
Mequitazine	18	90	67
Mizolastine	12.9 ± 4.5	98	1.4 ± 0.4
Terfenadine	16 - 23	98	2.2 - 2.9
Acrivastine[a]	1.7 ± 0.2	50	0.64 ± 0.13
Carebastine[a]	13 - 16	98	2.1 - 2.4
Cetirizine[a]	10	88-90	0.4
Fexofenadine[a]	18.3 ± 2.0	65	5.6 ± 0.7

a Zwitterionic drugs.
NA = not available.

sedation is defined and measured, and highlights the need to delineate as precisely as possible what is meant by terms such as sedation, drowsiness or sleepiness.

Sedation is an inner state; it may be defined as impairment of cognitive and psychomotor functioning and can be determined objectively through measures such as reaction time (RT). Drowsiness refers to an increased likelihood of falling asleep and commonly is assessed subjectively using the Stanford scale for sleepiness or visual analogue scales (VAS). Sleepiness refers to the same mental state as drowsiness; it can be subjectively measured using VAS or objectively measured by electrophysiological methods such as electroencephalogram (EEG). Psychomotor and perceptual function can be assessed objectively using actual or simulator driving, critical tracking, flicker fusion or auditory vigilance tests, whereas cognitive function can be tested by learning ability or information processing tasks.

However, the primary limitation of subjective assessments is that of bias, particularly given that the meanings of descriptors can change considerably over time, a phenomenon known as semantic drift. Patients may mislabel a state on the basis of suggestion or acquiescence and use words interchangeably which in fact describe different states. The measurement of the tendency of an antihistamine to cause sedation may be complicated further by the fact that these drugs can induce both subjective feelings of drowsiness and objective levels of cognitive and motor impairment. The fact that patients may be unaware of the latter two changes is a cause for concern if they must function normally during the day.

An additional problem concerning clinical trials with antihistamines is that only a certain percentage of patients report sleepiness (or somnolence), even when using classical first generation medications. To further complicate the picture, over a period of time many patients will develop tolerance to this adverse effect to a variable degree.[51,52]

Subjective reports and objective assessments of CNS effects are not always in agreement, which emphasises the distinction between the tendency of a drug to induce subjective drowsiness and its actual potential to influence CNS function and psychological aspects of performance. Thus, symptoms alone should not be relied upon to predict decrements in performance or alertness. A number of studies rely on the use of healthy volunteers to assess the psychoactive properties of antihistamines and individual variation in responses to these drugs might hamper the predictive quality of volunteer studies. In practice, however, any volunteer bias can be overcome by the introduction of a positive internal control whose effects should be demonstrable in any volunteer sample.[53,54]

Given the complexity of the potential CNS effects of antihistamines it can be appreciated that they cannot be reflected by a single measurement of impairment. Thus, a variety of objective and subjective methods of assessment are required to reliably evaluate the sedative effects of this class of drugs. When all these considerations are taken into account, the literature on the sedating properties of second generation antihistamines is not convincing. The currently available drugs need to be re-assessed for sedative effects using more powerful experimental designs which combine robust objective tests with subjective indices of sedation.

2.2 CNS Effects

There is a widespread tendency to consider the second generation antihistamines as being non-sedating medications. Indeed, when used at their recommended dosage in objective studies which used healthy volunteers, CNS depressant effects for both loratadine[55] and fexofenadine[56,57] appear to be no greater than those given by placebo. However, this issue is further complicated by evidence that sedation in allergic disease is a consequence of the condition itself leading to performance and learning impairment.[58-60] This fact raises concerns about claims of a risk-free sedation profile for certain antihistamines when these are often based on objective studies which used healthy volunteers.[61] Another issue is the tendency of patients with allergies to 'self medicate', titrating their antihistamine dosage upwards to achieve symptom relief.[62] In fact, if the dose of terfenadine,[63] loratadine[64] or cetirizine[65] is increased enough, sedation does occur. All of these considerations have led to several commentators[5,61,66-70] suggesting that the second generation antihistamines are more correctly termed as having minimal sedative effects when given at their recommended doses.

Of the currently available second generation drugs, there is much contention regarding the sedative potential of cetirizine. This was illustrated by a clinical study which investigated the efficacy of cetirizine in allergic rhinitis and reported a significant and dose-dependent increase in mild-to-moderate sleepiness (or somnolence) by cetirizine compared with placebo.[65] These findings have resulted in the suggestion by some that cetirizine should be regarded as a sedating antihistamine.[71,72] However, the logical conclusion of this approach would be the paradox of cetirizine being grouped with the sedating first generation drugs where it does not belong. This view is supported by the large number of clinical studies which have shown cetirizine to be both efficacious and well tolerated without significant subjective sedation for the treatment of rhinitis in adults[73-84] and in chronic urticaria.[85-90] Furthermore, cetirizine treatment has been reported to improve not only the symptoms of patients with allergic rhinitis but also their physical and social functioning, feelings of fatigue, general perception of health, physical and social limitations and their mental well-being.[91,92] Importantly, the safety of cetirizine has also been shown in the treatment of allergic rhinitis in children.[93-95] More recently, in the longest prospective safety study of any H_1 receptor antagonist conducted in any age group,[96] the safety of cetirizine was also shown in a group of 817 very young children (12 to 24 months old at study entry) with atopic dermatitis. There was a low drop-out rate and few adverse effects over the 18 months of the study, despite treatment of very young children with relatively high doses of cetirizine compared with those given to older children or adults. Furthermore, compared with placebo (396 children), cetirizine treatment (399 children) did not result in clinically relevant differences in growth or development or in neurological and cardiovascular symptoms. Importantly, this study demonstrated that neither fatigue nor somnolence were significantly higher in the cetirizine-treated group compared with the placebo-treated group.

Objective measurements offer a more robust assessment of the ability of a drug to cause sedation, although they are less sensitive than subjective measurements. Ramaekers and colleagues[97] reported that a single 10mg dose of cetirizine significantly affected actual driving performance by

Table IV. Objective testing of impairment or non-impairment of psychomotor performance after cetirizine treatment

Test	Impairment	No impairment
Actual driving test: coarse steering frequency, obstacle test, weaving index test	10mg[97]	10mg[3,53,102,103]
Computer-simulated driving test		10mg[97,53,104,105]
Multiple Sleep Latency Test (MSLT) with electroencephalographic potentials	10mg[98]; 15mg[98]	5mg[97,100]; 10mg[3,97,102,105]; 20mg [97,105]
P300-evoked electroencephalographic potential latency		10mg[106]
Visual function: dynamic visual acuity, critical flicker fusion		10mg[53,103,107,108]; 20mg[53,103]
Simple Reaction Time (SRT)		5mg[97]; 10mg[97,103-105, 109]; 20mg[97]
Choice Reaction Time (CRT)		10mg[3,107]
Vigilance tests	5mg[98]; 15mg[98]	5mg[97]; 10mg[97,105,110]; 20mg[97]
Simulated Assembly Line Tests (SALT)		10mg[99]
Stroop (word-colour) test		10mg[105,106]
Digit-symbol substitution		5mg[97,104]; 10mg[97,104]; 20mg[97]
Finger tapping		10mg[107]
Perceptual maze test		10mg[107]

healthy volunteers, and Nicolson and Turner[98] found that cetirizine 10 and 15mg led to shortened sleep latencies compared with placebo. However, several other studies have demonstrated no effect by cetirizine on daytime sleep latency at therapeutic doses.[99-101] Table IV illustrates data from a number of studies which examined the effect of cetirizine on objective measurements of psychomotor performance. However, as the majority of these studies used healthy volunteers, these data must be viewed in the light of the caveat mentioned above that the results may have been different if patients with allergic diseases had been studied. Thus, a question mark remains on this issue of cetirizine and sedation. It is acknowledged that this question might best be objectively answered by a meta-analysis of the available data. However, as discussed in this section, a major barrier to this approach is the lack of the use of standardised approaches to assess the psychometric measurements of antihistamines making a meta-analysis difficult to perform, a view also shared by others[66,72,111]

2.3 Cardiotoxicity

As previously mentioned, with a few exceptions, the second generation H_1 receptor antagonists have a highly lipophilic general structure which confers a high affinity for lean tissue[112] and which might account for some of the toxicity associated with some members of this class of drugs. Recently, the focus on the risk/benefit ratio of antihistamines has shifted from sedation to other adverse effects such as their potential to induce cardiac ventricular arrhythmias of the *torsades de pointes* type, first reported with astemizole[113] and later with terfenadine,[114] of which the latter drug has been the most widely prescribed. The European Commission has recently adopted a decision to withdraw some terfenadine preparations (120mg tablets and all terfenadine/pseudoephedrine tablet formulations) and the drug has also been withdrawn by the US Food and Drug Administration. Both astemizole and terfenadine rely on liver CYP for their metabolism to the therapeutically-active metabolite. Accumulation of unmetabolised terfenadine and astemizole can result in blockade of cardiac K^+ channels which regulate the duration of the action potential thereby prolonging the QT interval and resulting in life-threatening ventricular tachycardia.[115-118] Predisposing factors to the induction of cardiac arrhythmias by antihistamines include liver disease, concomitant prescribing of interfering drugs such as macrolides, overdose, congenital QT prolongation, ischaemic heart disease, congestive heart failure, or

electrolyte imbalance. Thus, in conditions of over dosage or when compromised liver function results in reduced metabolism, the plasma concentration of terfenadine or astemizole can rise which leads to cardiac toxicity through direct blockade of a K^+ channel expressed by the cardiac ventricular myocyte.

The possibility that cardiotoxicity is an adverse effect common to all second generation antihistamines has been discounted.[119,120] Although fexofenadine, the active metabolite of terfenadine, appears to be free of any adverse cardiovascular effects,[120] fexofenadine therapy was associated with QT lengthening and life-threatening arrhythmias in a single case report of a patient with mild hypertension and mild left ventricular hypertrophy.[121] This case indicates that fexofenadine may increase the QTc time and induce ventricular arrhythmias in susceptible patients. As discussed in section 1.1, drug interactions occur with agents other than astemizole and terfenadine. However, conflicting results have been noted in guinea pigs and rabbits with loratadine,[122], terfenadine, astemizole, ebastine, cetirizine, carebastine and norastemizole.[123-125] In addition to the conflicting findings with loratadine and concomitant medication described in section 1.1,[31,32] two studies have demonstrated that neither loratadine[126] nor acrivastine[127] prolonged QTc interval in healthy volunteers.

Cetirizine appears to be free of any cardiovascular adverse effects.[119] Healthy volunteers who were treated for 7 days with up to 6 times the recommended daily dosage of cetirizine did not show any lengthening of the QTc interval when compared with healthy volunteers taking placebo.[128] Moreover, an accidental massive overdose of cetirizine in an 18-month-old child did not cause any adverse cardiac or neurological reactions.[129] In a clinical study, Delgado and coworkers[130] investigated the cardiac effects of recommended doses of terfenadine, astemizole, loratadine and cetirizine in children treated for perennial allergic rhinitis; treatment was given alone or concomitantly with erythromycin. No significant changes in the QT interval or QTc were observed among children who received astemizole, loratadine or cetirizine, with or without erythromycin. Children who had received terfenadine and erythromycin showed significantly prolonged QT intervals, although analysis of the QTc interval revealed no significant differences in this group. Furthermore, in a recent pharmacosurveillance study which determined the heart rhythm disorders and cardiac deaths for some of the most common nonsedating antihistamines, cetirizine displayed the lowest adverse drug reaction report rate per million of defined daily doses sold for all adverse events; however, the study should have included a control group not taking antihistamines in whom rates of spontaneous cardiac events could have been quantified.[131]

2.4 Interaction with Cardiac Potassium Channels

Recent evidence has demonstrated that the cardiotoxic manifestations associated with astemizole and terfenadine may be explained by their ability to interfere with the cardiac repolarising current IKr.[117,132] These particular K^+ channels are encoded by the human ether-a-gogo-related gene (*HERG*)[133,134] and both astemizole and terfenadine have been shown to block HERG K^+ channels with nanomolar affinity.[135,136] The possible interaction of antihistamines with HERG K^+ channels can be studied either in cells in which these channels are constitutively expressed (such as cardiac myocytes or human neuroblastoma cells)[137] or upon their heterologous expression in other cellular systems. An expression system commonly used by pharmacologists studying ion channels is the *Xenopus* oocyte, which can be microinjected with *in vitro*-transcribed RNA derived from HERG cDNA. These cells can be used for electrophysiological study of the heterologously expressed HERG K^+ channels by means of the 2 microelectrode voltage clamp technique.

This technique was recently applied to compare the effect of terfenadine, astemizole, loratadine and cetirizine on the inhibition of HERG K^+ channels expressed in *Xenopus* oocytes.[138] Both

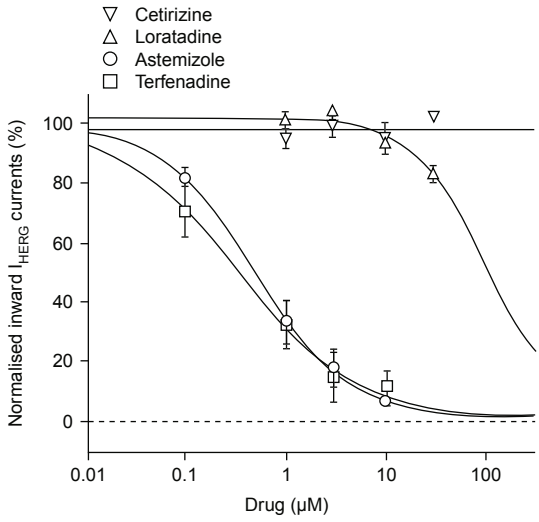

Fig. 3. Dose-response curve for human ether-a-gogo-related gene (*HERG*) K^+ channel block expressed in *Xenopus* oocytes by four second-generation antihistamines. The inward HERG K^+ tail currents recorded in *Xenopus* oocytes upon repolarisation to -100mV after depolarising pulses of 2 seconds to 0mV were normalised to the control value and expressed as a function of drug concentration. The solid lines represent the fit of the experimental data to the following binding isotherm: y = max/(1+X/IC50)n, where X is the drug concentration and n the Hill coefficient. Fitted values for n were between 0.72 and 0.96. Each point is the mean (S.E.M.) of 3 to 6 determinations (reproduced from Taglialatela et al.,[138] with permission).

astemizole and terfenadine had potent blocking effects whereas cetirizine had no measurable effect in concentrations up to 30 μmol/L. On the other hand, the same concentration of loratadine caused a 20% blockade of I_{HERG}. Given the high drug concentrations required to exert these effects, the clinical relevance of loratadine's action may be questioned. These findings are summarised in figure 3. Similar results were obtained from experiments which utilised constitutively expressed HERG channels in SH-SY5Y human neuroblastoma cells (fig. 4). Again, cetirizine failed to affect I_{HERG}, whereas terfenadine and astemizole had potent blocking effects with a lesser effect observed for loratadine. A similar study also demonstrated that high concentrations of loratadine above the therapeutic level had a blocking effect on the human cardiac Kv1.5 channel which was cloned from human ventricle and stably expressed in a mouse cell line.[139] Thus, the results of these studies suggest that cardiotoxic potential is not a property common to all second generation antihistamines as they display marked heterogeneity in their ability to block cardiac K^+ channels.

In summary, it might be argued that the incidence of cardiotoxic effects is negligible in view of the widespread use of antihistamines on a worldwide basis. However, it must be remembered that these drugs are used to treat non-life–threatening conditions and several of the drugs currently available are extremely efficacious while being free of any serious cardiotoxic risk. Furthermore, many antihistamines are available without prescription and concomitant use of macrolides by patients taking antihistamines is common, particularly in groups vulnerable to high levels of respiratory tract infections such as infants and children. In such situations it might be preferable to offer an antihistamine whose pharmacokinetic profile is not modified by the use of antibacterials.

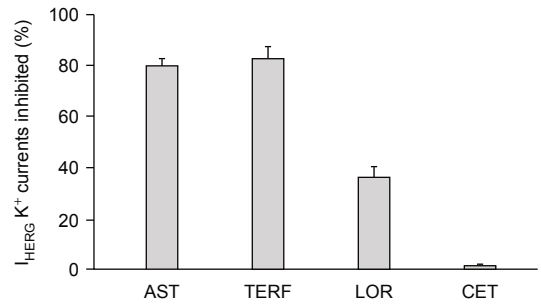

Fig. 4. Effect of the 4 different H_1 receptor antagonists astemizole (AST), terfenadine (TERF), loratadine (LOR) and cetirizine (CET) on I_{HERG} constitutively expressed in SH-SY5Y human neuroblastoma cells. The same experimental protocol (holding potential: -60mV; test potential: 0mV for 10 sec; return potentials: from 0 to -140/-180mV in -20mV steps for 100ms) was performed in several SH-SY5Y cells in control conditions and after 5 min perfusion with each H_1 receptor antagonist (3 μmol). Drug effects are reported as percent of inhibition of the inward I_{HERG} current at -140 mV, without leak subtraction. Each value is the mean (S.E.M.) of 4 determinations for each drug (reproduced from Taglialatela et al.,[138] with permission).

3. Anti-Inflammatory Effects in Allergic Inflammation

The mechanisms responsible for the accumulation of pro-inflammatory cells at tissue sites of allergic inflammation are complex but probably involve a combination of selective adhesion of cells to post-capillary venular endothelium, followed by transmigration into the tissues under the influence of chemotactic factors including lipid mediators, cytokines and chemokines. Once in the tissues there is an elaborate interaction between infiltrating cells, resident cells, and the mediators and cytokines released as part of the inflammatory response. The cells that are important in these processes include those recruited to the inflammatory site such as T cells, eosinophils, mast cells, monocytes, basophils and platelets in addition to resident cells such as antigen presenting cells, epithelial cells and endothelial cells. Thus anti-allergic effects might include inhibition of cell migration, mediator release, adhesion and adhesion molecule expression. It has been recognised for some years that, in addition to being potent antihistamines, a number of the second generation drugs appear to possess several anti-allergic effects which cannot be explained by antagonism of the H_1 receptor. Thus, they may play an enhanced role in treating allergic disease if, in addition to antagonising the effects of histamine, they also inhibit the influx and/or activation of pro-inflammatory cells. In general terms, these studies can be divided into *in vitro* effects on the function of isolated pro-inflammatory cells or *in vivo* effects where the impact of a given drug on inflammatory parameters is assessed in addition to its effects on symptom relief.

3.1 *In Vitro* Studies

Examination of the literature reveals an almost bewildering number of studies on the anti-inflammatory effects of antihistamines *in vitro* (for a comprehensive review see Church et al.[140]). Many of these have concentrated on examining the ability of the second generation drugs to prevent or inhibit mediator release from diverse cell types including mast cells, basophils, eosinophils and neutrophils. However, on closer examination many of the studies which reported a significant effect on inflammatory cell function used drug concentrations which were hundreds or in some cases thousands of times higher than those that can be achieved *in vivo*. Indeed, Church[141] has recently pointed out that, with some exceptions, the majority of the non-H_1 receptor-mediated effects of antihistamines require higher concentrations than would be expected to occur in clinical practice. However, it must also be remembered that most of the *in vitro* studies of anti-inflammatory effects by antihistamines used pharmacological doses of agonists which are likely to be far greater than those reached in the tissues. These effects would have to be overcome by correspondingly higher concentrations of the antihistamine under test. An additional consideration is that if high concentrations are required *in vitro*, any inhibitory effect might merely be a consequence of drug toxicity. This question is almost impossible to answer as few studies addressed the issue of the effect of the test drug on the viability of the cells under examination.

Therefore, with these considerations in mind and for the sake of clarity, table V has been limited to listing those studies in which significant inhibitory effects on inflammatory cell function were observed with drug concentrations which are equal to or lower than the therapeutic plasma concentration of the antihistamine under examination. This approach reduced the number of studies published on *in vitro* anti-inflammatory effects of second generation drugs from over 100 to around 40. This information is presented with 2 caveats: first, local levels of antihistamines may be higher at tissue sites such as in the nose than in the plasma; and secondly certain antihistamines might preferentially accumulate in inflammatory cells *in vivo*. However, there is no current evidence to support either notion.

It can be seen from table V that the majority of the second generation antihistamines have at least some inhibitory effects on mediator release from diverse cell types, all of which appear to be inde-

Table V. *In vitro* anti-inflammatory effects of antihistamines at relevant concentrations

Cetirizine

Inhibited fMLP-, PAF-,[142,143] LTB_4-, IL-8– or C5a-[144]dependent eosinophil chemotaxis

Significantly inhibited LTB_4- and fMLP-dependent monocyte chemotaxis[145]

Inhibited PAF-induced human eosinophil hyperadherence to endothelial cells[144]

PAF-induced neutrophil and eosinophil enhanced eosinophil cytotoxicity and complement- or IgG-dependent rosette formation[146]

Decreased eosinophil membrane heterogeneity and blocked PAF-induced membrane fluidity changes[147]

Inhibited PAF-dependent superoxide generation by eosinophils isolated from patients with allergies[148]

An inhibitory effect on LTB_4 production by isolated human neutrophils[149]

Inhibition of LTB_4 generation by fMLP- or NaF-stimulated neutrophils[150]

Enhanced release of PGE_2 from human monocytes and rat peritoneal macrophages[151]

Inhibited IFNγ-mediated upregulation of ICAM-1 expression by primary cultures of human nasal epithelial cells[152]

Inhibited PMA- or TNFα-stimulated IL-8 release from human epithelial cells by reducing IL-8 gene expression[153]

Inhibited LTB_4, arachidonic acid and phospholipase A2 release from human PMN, ΔF508 cells, CHO cells and rabbit chondrocytes stimulated with different agonists [fMLP, NaF, A-23187, bradykinin, epinephrine (adrenaline) or IL-1][154]

Calcium ionophore-dependent release of TNFα from a human mast cell line or mononuclear cells inhibited by μmol concentrations of cetirizine[155]

Loratadine

Calcium ionophore-dependent release of TNFα from human mast cell line or mononuclear cells inhibited by μmol concentrations of loratadine[155]

Inhibited PAF-induced eosinophil chemotaxis and O_2-generation[156]

Inhibition of histamine-induced endothelial cell expression of P-selectin and secretion of IL-6 or IL-8[157]

Inhibited ionophore- and antigen-dependent leukotriene release from human lung[158]

Elevates cytosolic Ca^{2+} in rat peritoneal macrophages or human platelets[159]

Inhibited mitogen-induced mononuclear cells and allergen-induced T cell proliferation[160]

Significantly ablated platelet aggregation and histamine release induced by anti-IgE[161]

Desethoxycarbonyl-loratadine inhibited IgE- and A-23187–induced leucocyte histamine release[162]

Increased mRNA expression for the anti-inflammatory cytokine IL-10 in cultured normal human keratinocytes[163]

Desloratadine inhibited PAF-induced eosinophil chemotaxis, eosinophil adhesion to endothelial cells stimulated with TNFα and PMA-induced eosinophil superoxide generation[164]

Incubation of cultured human bronchial epithelial cells with loratadine significantly attenuated the NO_2-induced release of RANTES and sICAM-1[165]

Terfenadine

Inhibition of mediator (LTC_4/D_4) and cytokine (TNFα and GM-CSF) release from nasal polyp cells[166]

Inhibited PAF- and fMLP-dependent eosinophil and neutrophil chemotaxis[167]

Inhibited IgE-dependent mediator release histamine and PGD_2 release from lung and skin mast cells[168]

Fexofenadine

Inhibited GM-CSF and sICAM-1 release by epithelial cells cultured with eosinophils and latex beads[169]

Inhibited histamine-induced release of TNFα and β-glucuronidase by human lung macrophages[170]

Reduced ICAM-1 expression by a conjunctival epithelial cell line and fibroblast cell line and blocked IL-6 release by fibroblast cell line[171]

Calcium ionophore (A-23187)–induced eosinophil cationic protein release inhibited by low (<1 μmol) concentrations of fexofenadine[172]

Astemizole

Inhibited histamine release by rat peritoneal mast cells or by lung fragments in sensitised guinea pigs[173]

Mequitazine

Prevented fMLP- and PMA-induced O_{2-} generation from rat neutrophils[174]

Clemastine

Inhibited neutrophil superoxide radical generation[175]

Azelastine

Inhibited PAF synthesis and release from neutrophils,[176,177] alveolar macrophages[178] and eosinophils[179] and prevented eosinophil superoxide radical production[180,181]

Table V. Contd

Suppressed TNFα secretion by rat mast cell line[182] and cultured mouse mast cells[183]
Inhibited PGE_2 production by IL-1 stimulated cultured human skin fibroblasts[184]
Inhibits calcium-ionophore–dependent generation of LTC_4 and LTB_4 in rat basophilic leukaemia cells[185]
Blocks activation of NF-κB, IL-1α, IL-6, GM-CSF and TNFα mRNA in leucocytes and monocytes[186]
Oxatomide
Inhibited eosinophil[187] and neutrophil[188] superoxide radical generation

C5a = 5th complement component (anaphylatoxin); **CHO** = chinese hamster ovary; **fMLP** = f-Met-Leu-Phe; **GM-CSF** = granulocyte macrophage-colony stimulating factor; **ICAM** = intracellular adhesion molecule; **IFN** = interferon; **Ig** = immunoglobulin; **IL** = interleukin; **LTB_4, LTC_4, LTD_4** = leukotrienes B_4, C_4, D_4; **NaF** = sodium fluoride; **NF-κB** = nuclear factor kappa B; **NO_2** = nitrogen dioxide; **PAF** = platelet-activating factor; **PGD_2, PGE_2** = prostaglandins D_2, E_2; **PMA** = phorbol myristate acetate; **PMN** = polymorphonuclear leucocyte; **RANTES** = growth factor (Regulated on Activation, Normal T cell Expressed and Secreted); **sICAM-1** = soluble ICAM-1; **TNF** = tumour necrosis factor.

pendent of the potent H_1-blocking abilities of this class of compounds. Additionally, azelastine, loratadine, terfenadine and cetirizine have all been reported to inhibit chemotaxis of eosinophils *in vitro*. These are potentially important observations as it is now well established that the eosinophil is a key effector cell in the pathogenesis of allergic inflammation.[189] In addition, cetirizine inhibited neutrophil and monocyte chemotaxis and also appears to have particular effects on other eosinophil functions[190] as well as on other cell types.[191]

Interestingly, the antihistamine dexchlorpheniramine had no effect on f-Met-Leu-Phe (fMLP)– or platelet-activating factor (PAF)–induced eosinophil chemotaxis, an observation supporting the notion that inhibitory effects on eosinophil chemotaxis by second generation drugs cannot be attributed to H_1 receptor blockade. However, there is a paucity of data which would allow a definitive answer with regard to the underlying cellular mechanisms responsible for these *in vitro* anti-inflammatory effects by several second generation drugs. The cationic amphophilic nature of many antihistamines suggests that they might form an association with cell membranes thereby inhibiting calcium binding and the action of membrane associated enzymes.[141] For example, one study demonstrated an inhibitory effect by azelastine on eosinophil chemotaxis. This effect was observed only under conditions of low calcium concentration (0.6 mmol/L) and was abolished by higher calcium concentrations (3.0 mmol/L), suggesting that azelastine may exert its anti-inflammatory effects by inhibiting calcium entry into cells.[192]

A final consideration regarding the *in vitro* studies is that, of the currently available drugs, only acrivastine, fexofenadine and cetirizine are not metabolised *in vivo*; this fact raises additional doubts as to the relevance of the *in vitro* testing of compounds reliant on biotransformation to the active metabolite, although some studies have examined the anti-inflammatory effects of a number of active metabolites (table V).[140,141]

3.2 *In Vivo* Studies

Of potentially greater interest is the demonstration of an anti-inflammatory effect by an antihistamine *in vivo* as this is far more therapeutically relevant than the *in vitro* studies. Although the ability of antihistamines to exert anti-allergic effects in humans has been appreciated for some time,[193] the question of whether this enhances the therapeutic effect of an antihistamine has been the subject of much debate. It is difficult to give a definitive answer owing to the problems inherent in isolating the many anti-inflammatory effects from the H_1-blocking effect of a given drug. Notwithstanding this, however, demonstrable suppressive effects on allergic inflammation which are additional to potent H_1 receptor blockade can only be seen as a positive attribute for a drug. Examination of the literature reveals a large number of *in vivo* studies in which anti-inflammatory effects by the second generation compounds have been reported and these are presented in table VI.

Table VI. *In vivo* anti-inflammatory effects of antihistamines (negative studies in italics)

Drug	Effects on cell accumulation	Effects on adhesion molecule expression	Effects on other inflammatory events
Cetirizine	Inhibition of eosinophil accumulation in atopic skin challenged with pollen[194-198] or PAF[199] *No significant effect on Ag-induced cutaneous LPR, some reduction in eosinophil numbers*[201,202] Reduced symptoms and eosinophils and neutrophils accumulation in conjunctival challenge-induced EPR and LPR[200] Inhibited EPR to antigen. *No effect on LPR, cellular responses nor lactoferrin and ECP*[208,209] Inhibited Ag-induced eosinophil recruitment in nose,[212] lung,[213] protective effect on asthmatic LPR[214] *No effect on allergen-induced eosinophil accumulation in nose*[217] Reduced eosinophilia in bronchial challenged monkeys,[220] the ovalbumin-[221] or PAF[222]-induced rat pleural cavity eosinophilia, Ag-induced eosinophil influx into the trachea of dogs[223] Decreased eosinophil and neutrophil infiltration and ECP and EPO in nasal lavage from patients with allergic rhinitis[95,225]	Reduced epithelial ICAM-1 expression associated with conjunctival challenge-induced EPR and LPR[200] Reduced nasal epithelium ICAM-1 expression, in patients with asthma[203] Reduced nasal epithelium ICAM-1 expression in nasal polyposis patients[205] Reduced levels of soluble ICAM-1 in nasal lavage[210] Modulated keratinocyte ICAM-1 and HLA-DR in psoriatic plaques[215] Decreased ICAM-1, sICAM-1 in nasal lavage of patients with allergic rhinitis[218]	Inhibited *ex vivo* monocyte chemotaxis[145] Modulated *ex vivo* sulfido-leukotriene production by leucocytes challenged with Dp antigen[204] Inhibited codeine-induced wheal and flare[206] and flare response to bradykinin[207] Inhibited kallikrein-induced LPR in patients with urticaria[211] Inhibited bradykinin-induced wheal and flare in atopic and healthy individuals[216] *No effect on* ex vivo *neutrophil chemotaxis or O_2- production in healthy individuals*[219] Reduced nasal TAME-esterase activity and LTC_4[224] Inhibited bradykinin-induced skin reactions[226] Reduced histamine and tryptase in nasal secretions after allergen challenge[227]
Loratadine	Reduced eosinophil and metachromatic cells, ECP, EPO and histamine in nasal secretions[228] In combination with flunisolide significantly reduced eosinophilia in patients with non-allergic rhinitis with eosinophilia[233] *No effect on PAF-induced eosinophil influx into skin of urticaria patients*[232] *No significant inhibition of skin reactions induced by histamine and grass pollen, nor eosinophil accumulation[198]* *No effect on anti-IgE-mediated histamine release or leucocyte accumulation in skin [237]*	Reduced epithelial ICAM-1 expression following conjunctival challenge[229,230] Reduced ICAM-1 on nasal epithelium following natural exposure to allergen[228]	*No effect on codeine-induced histamine release in normal skin*[231] *or kallikrein-induced LPR in urticaria patients*[232] Decreased numbers of IL-2R+, HLA-DR+ PCNA in allergic rhinitis mucosa[234] Reduced levels of tryptase and α2-macroglobulinin allergen-induced nasal secretions[235] Inhibited pollen-induced histamine and PGD_2 release in nasal secretions[236] Reduced TAME-esterase and histamine levels in allergen-induced nasal secretions[238]
Terfenadine	Reduced inflammatory cell infiltration during conjunctival provocation test[239] Reduced inflammatory cells and ECP in allergic rhinitis mucosa[240] *Allergic bronchial eosinophilia in guinea pigs was inhibited by orally administered dexamethasone and methylprednisolone but not by terfenadine*[241] *No effect on leucocyte infiltration in response to cutaneous antigen challenge*[242]	Reduced ICAM-1 expression associated with conjunctival provocation test[239] Reduced nasal epithelial ICAM-1 in allergic rhinitis mucosa[240]	Inhibited flare response to bradykinin - little effect on wheal[216] Inhibited pollen-induced histamine and PGD_2 release in nasal secretions[236] Significantly inhibited cutaneous IgE-mediated inflammatory lesion size[242] Reduced nasal histamine release, kinin levels, and TAME-esterase activity[243]

Table VI. Contd

Drug	Effects on cell accumulation	Effects on adhesion molecule expression	Effects on other inflammatory events
Fexofenadine	In a murine model of allergic sensitisation inhibited methacholine-induced airway hyperresponsiveness with no effect on eosinophilic inflammation[244] Inhibited early and late reaction to cutaneous allergen-challenge[246]	No effects reported to date	Inhibited antigen-induced bronchospasm in sensitised guinea-pigs and histamine release from rat peritoneal mast cells[245] *No effect on IL-4, IL-10, TNF, MIP-1α or GM-CSF in nasal secretions of patients after nasal antigen challenge*[247]
Ebastine	Prophylactic against immediate mosquito bite symptoms[248]	No effects reported to date	Inhibited nasal GM-CSF in Ag-challenged patients with rhinitis[249]
Astemizole	Inhibition of eosinophil influx into the trachea of antigen challenged dogs[223]	No effects reported to date	No effects reported to date
Mizolastine	Inhibited AA-induced rat paw inflammation,[250] and colitis[251] and ICAM-1 expression on airway stromal cells[252]	Inhibited soluble ICAM-1 secretion in antigen-challenged human skin[253]	Inhibited leukotriene release by leukocytes stimulated with sera from patients with chronic urticaria[254]
Azelastine	Treatment of atopic asthmatics reduced bronchial mucosal EG2+ eosinophils and T cells[255] Inhibition of eosinophil influx in trachea of antigen challenged dogs[223] Reduced conjunctival EPR/LPR and inflammatory cell infiltration[256] Decreased nasal symptoms, eosinophils and neutrophils in EPR and LPR[257] Inhibited PAF-induced microvascular leakage in rats without affecting neutrophil accumulation[261]	Reduced conjunctival ICAM-1 expression[256] Decreased ICAM-1 expression by nasal epithelial cells in EPR and LPR[257]	Reduced histamine and tryptase in nasal secretions after allergen challenge[227] Reduced substance P in nasal secretions from patients with rhinitis[258] Inhibited guinea-pig leukotriene-mediated lung anaphylaxis[259] Reduced conjunctival nonspecific hypereactivity[260] Reduced levels of IL-4 and soluble CD23+ in patients with nasal allergy[262] Reduced late-phase reactions to skin-prick with allergen[263]
Oxatomide	Inhibited conjunctival EPR, LPR, inflammatory cells & ICAM-1[264]	Inhibited conjunctival ICAM-1 expression following antigen challenge[264]	Reduced substance P in nasal secretions from patients with rhinitis[258]

AA = arachidonic acid; **Ag** = antigen; **Dp** = Der PI (house dust mite); **ECP** = eosinophil cationic protein; **EPO** = eosinophil peroxidase; **EPR** = early-phase reaction; **GM-CSF** = granulocyte macrophage-colony stimulating factor; **HLA-DR** = human leucocyte antigen (DR locus); **ICAM-1** = intracellular adhesion molecule; **Ig** = immunoglobulin; **IL** = interleukin; **LPR** = late-phase reaction; **LTC_4,D_4** = leukotrienes C_4, D_4; **MIP-1α** = macrophage inflammatory protein-1 alpha; **PAF** = platelet-activating factor; **PCNA** = proliferating cell nuclear protein?; **sICAM-1** = soluble ICAM-1; **TAME** = alpha-N-p-tosyl L-arginine methyl ester; **TNF** = tumour necrosis factor.

In terms of anti-inflammatory effects *in vivo*, studies which have observed positive inhibitory effects by treatment with cetirizine on cell accumulation, adhesion molecule expression or mediator release are far more numerous than for any other drug in the same class. Perhaps the most striking effects by cetirizine were on the inhibition of eosinophil accumulation at skin sites challenged with pollen[194-198] or PAF.[199] This effect could not be attributed to the activity of cetirizine at the H_1 receptor since cetirizine does not block histamine-induced eosinophil infiltration and astemizole did not have any effect on eosinophil migration. Furthermore, neither promethazine nor chlorphenamine induced any alteration in allergen-induced inflammatory cell infiltration.[197] Moreover, loratadine treatment had no effect on eosinophil influx in response to an intradermal injection of PAF

in patients with urticaria and did not influence the pollen-induced skin reactions or eosinophil influx seen in sensitive individuals.[198] In addition, use of the skin chamber technique failed to demonstrate a significant effect for loratadine on inflammation, histamine release or recruitment of eosinophils or other leucocytes to skin sites in patients with atopy challenged with anti-IgE.[237]

Considerable debate has been generated by more recent studies which re-evaluated the effect of cetirizine on allergen-induced cutaneous late-phase reaction (LPR) in patients with atopy. Two of these used punch biopsies rather than skin windows to study the nature and extent of the cellular infiltrate.[201,202] In neither study did pre-treatment with cetirizine significantly inhibit the magnitude of the cellular infiltrate during the LPR, although both studies demonstrated a reduction in eosinophil numbers in some patients. In contrast, prednisolone pre-treatment of these patients significantly decreased both the magnitude of the LPR and eosinophil influx.[201,202] The discrepancies between the skin window and biopsy studies might in part be explained by methodology, for instance the quantity and purity of the allergens necessary to induce a LPR in all patients. Furthermore, the skin window technique enumerates and identifies cells that have undergone transendothelial migration and, thus, have left the dermal post-capillary venules, whereas biopsies measure the gross cellular content at the reaction site. This difference is a potentially important one since cetirizine might exert its effect by inhibiting eosinophil adhesion to and/or migration across the microvascular endothelium. However, further studies which utilised the skin window technique and biopsies to evaluate allergen-induced, late-phase, cutaneous, allergic inflammatory cell accumulation found that this was unaffected by cetirizine treatment.[208,209] These negative findings might be explained by the fact that in the later studies the 6-hour time-point was chosen to evaluate the effect of cetirizine on the LPR, whereas the earlier studies only demonstrated a significant effect by cetirizine at 8 hours or later.[194,195]

Epithelial adhesion molecule expression is thought to represent an important mechanism by which these cells interact with other pro-inflammatory cells and its modulation might result in clinical benefit. For example, a conjunctival challenge of allergic patients resulted in an increase in epithelial cell intracellular adhesion molecule-1 (ICAM-1) expression and a large increase in the total number of inflammatory cells at the challenge site at 30 minutes; the effect persisted for up to 24 hours and these changes paralleled the increase in symptoms.[165] In several double-blind, randomised and placebo-controlled trials oxatomide, cetirizine, loratadine and terfenadine reduced epithelial ICAM-1 expression, eosinophil and neutrophil numbers and the clinical symptoms associated with both the early-phase reaction (EPR) and LPR to a conjunctival challenge.[200,229,239,264] In a further double-blind, placebo-controlled, randomised, parallel study of children with allergic asthma associated with mite sensitivity, cetirizine treatment resulted in a significant reduction and in some cases a total absence of ICAM-1 expression by nasal epithelial cells, which was associated with a trend towards a reduction in eosinophil and neutrophil numbers.[203]

An obvious question that arises from the observations presented in tables V and VI is whether such properties are shared by all members of the second generation antihistamines, that is, whether this is a class effect or is confined to certain members of the second generation drugs. Although the widely differing chemical structures of antihistamines does suggest that these effects are rather nonspecific, only carefully conducted, large scale, comparative studies would allow this question to be answered with confidence. An additional question is whether such effects are therapeutically relevant and, if so, whether they may enable us to distinguish further between these compounds. One final issue that remains to be clarified is the dissection of the mechanisms by which these drugs exert their anti-inflammatory effects, information which might facilitate the development of more effective anti-inflammatory therapy.

4. Clinical Considerations

Oral antihistamines have for many years been first-line, highly effective medications for the treatment of allergic hypersensitivity reactions such as hay fever and urticaria. Most patients do not use their antihistamines on a regular basis and usually expect fast symptomatic relief from their allergies without undesirable adverse effects. In particular, the second generation drugs are highly effective treatments for allergic rhinoconjunctivitis in which they give rapid relief from rhinorrhoea, sneezing and itching.[266,267] However, in general, they have only a minor effect on nasal obstruction, which is most probably because histamine is not the main cause of nasal obstruction. Other mast cell-derived mediators released during the anaphylactic response probably play a part in these reactions and these include prostaglandins, neuropeptides and leukotrienes. Nasal corticosteroids have an effect on nasal obstruction and a recent meta-analysis confirmed that they are superior to antihistamines in the treatment of rhinitis.[268]

4.1 Comparison of the Potency of Antihistamines

One method which is useful when considering the effectiveness and onset of action for an antihistamine is to assess its ability to block the *in vitro* intradermal histamine-induced wheal and flare reaction in the skin. Histamine can be either injected intradermally or administered by skin-prick test. In one double-blind, crossover study cetirizine 10mg, terfenadine 60 and 120mg, loratadine 10mg, astemizole 10mg and chlorpheniramine 4mg were compared with placebo for their ability to suppress histamine-induced skin wheal and flare reactions. Cetirizine was the only agent which gave greater than 50% inhibition of the area of wheal and flare 24 hours after administration.[269] In a more recent study,[270] cetirizine was found to be more consistent than ebastine in suppressing cutaneous reactivity to histamine in healthy volunteers. This finding might be a reflection of the need for ebastine to be metabolised into the active carebastine whereas the effect of cetirizine is not dependent on biotransformation. In a direct comparative study, cetirizine was equipotent to loratadine, administered at 4 times the recommended dose, in suppressing histamine-induced wheal and flare;[271] it was also superior to both loratadine[272] and ebastine[273] in reducing cutaneous blood flow as assessed by laser Doppler flowmetry. More recently, fexofenadine has been shown to be both efficacious and well tolerated for the treatment of allergic rhinitis[274,275] and chronic idiopathic urticaria.[276] In terms of its ability to block histamine-induced wheal and flare reactions, fexofenadine was found to be very effective and to have a more rapid onset of action than loratadine.[277]

A recent study further emphasises the potential differences between members of the second generation class of drugs. This double-blind crossover study compared cetirizine, ebastine, epinastine, fexofenadine, terfenadine and loratadine with placebo for suppression of the histamine-induced wheal and flare. Epinastine had the most rapid onset of action followed by cetirizine, while terfenadine induced potent inhibition which was superior to its metabolite fexofenadine. The rank order of inhibitory effect was cetirizine, epinastine, terfenadine, ebastine, fexofenadine, loratadine and placebo. 13 of 14 patients showed greater than 95% inhibition of wheal area by cetirizine; just 6 of 14 had a similar response after treatment with terfenadine, epinastine and ebastine; 5 of 14 after fexofenadine; and 2 of 14 following loratadine treatment.[278] These findings suggest that if it is assumed that these antihistamines exhibit comparable receptor affinities, then cetirizine appears to have superior dermal bioavailability.

4.2 Antihistamine Use in Asthma

Histamine is also a mediator implicated in asthma pathogenesis, causing smooth muscle contraction, mucus hypersecretion and increased vascular permeability leading to mucosal oedema; moreover, bronchial hyperresponsiveness to histamine is a well known feature of asthma. Inhalation of histamine will produce dose-dependent bronchial con-

striction which is greater in people with asthma than those without. Histamine concentrations in bronchoalveolar lavage (BAL) from patients with allergic asthma are higher than those from patients with allergic rhinitis or healthy individuals, and histamine can contribute to the hyperreactivity seen in patients with asthma.[279,280] Many patients with asthma show an enhanced ability to release histamine spontaneously in the peripheral circulation and lungs compared with healthy individuals as a result of increased peripheral basophil and mast cell degranulation. Those patients receiving effective asthma medication release less histamine than those not receiving treatment.[281] Segmental antigen challenge of healthy volunteers and people with asthma demonstrated increased histamine levels and increased bronchoconstriction in the challenged area in the group with asthma[282] and increased levels of histamine in BAL fluid were associated with increased hyperresponsiveness following methacholine challenge.[283]

The potential therapeutic efficacy of antihistamines in asthma would therefore appear to be considerable. However, the use of the early antihistamines in asthma treatment was limited because they were not effective at the doses recommended for treatment of allergic rhinitis whereas higher doses resulted in intolerable adverse effects.[284] What then is the evidence that some of the newer antihistamines might be useful as adjunct therapy in allergic asthma, particularly as it is now recognised that inflammation of the airways is a key pathogenic event in asthma and, as discussed in section 3, many of the second generation drugs have documented anti-inflammatory effects?

Although it is acknowledged that antihistamines cannot be considered to be first-line medications for asthma therapy, a number of studies have evaluated the potential of some second generation antihistamines as adjunct therapies.

For example, Wood-Baker and Holgate[285] compared the inhibition of bronchospasm, induced by inhalation of histamine or methacholine, by astemizole, brompheniramine, cetirizine, chlorpheniramine, clemastine, cyproheptadine, terfenadine and placebo in a single group of patients with asthma. Compared with placebo, all the antihistamines provided significant protection against histamine-induced bronchoconstriction as determined by the histamine PC_{20} (provocative concentration producing a 20% decrease), with cetirizine giving the greatest protection. None of the drugs tested was protective against the effects of methacholine-induced constriction.

In patients with atopic asthma, ebastine,[286] cetirizine and loratadine[287] effectively reduced the bronchial response to a histamine challenge. In contrast, a double-blind, placebo-controlled, crossover study with 10 patients with mild asthma found that cetirizine had no significant effect on PAF-induced bronchoconstriction.[288] In responding patients with atopic asthma, cetirizine inhibited cellular recruitment 24 hours after allergen inhalation challenge in terms of total numbers of inflammatory cells in the bronchial wash and with a particular effect on eosinophil recruitment.[213]

Wasserfallen et al.[214] found that cetirizine had no effect on the EPR to antigen but had a significant protective effect on the LPR to allergen bronchial challenge whereas, in contrast, Bentley and coworkers[289] failed to demonstrate an inhibitory effect by cetirizine on either the early- or late-phase asthmatic reactions to inhaled allergen in sensitised patients.

Treatment of patients with pollen-associated asthma using cetirizine 15mg daily for 2 weeks produced a marked lowering of pulmonary symptoms associated with a decrease in the use of other medications including β_2 agonists and corticosteroids compared with the placebo group.[290] Bousquet et al.[291] found cetirizine 10 or 15mg twice daily to be more effective than terfenadine 60mg twice daily in the control of seasonal asthma symptoms in 97 patients allergic to grass pollen with recent onset mild asthma. A similar study also concluded that cetirizine could prevent exacerbation of seasonal asthma caused by grass pollen.[292] In contrast, Rafferty et al.[293] were unable to demonstrate a significant protective effect by either oral or inhaled cetirizine on allergen-induced early broncho-

constriction in a double-blind, randomised, placebo-controlled trial, and a similar study demonstrated only a nonsignificant tendency for cetirizine to protect against the allergen-induced immediate asthmatic response.[294]

Azelastine 4 mg/day for 3 months in 13 patients with asthma resulted in significant improvements in asthma symptoms accompanied by a reduction of activated eosinophils and T cells in the bronchial mucosa compared with the placebo-treated group, and significant correlations were found between clinical data and immunohistochemical parameters.[255] Moreover, azelastine 6mg twice daily reduced the need for inhaled corticosteroids in patients with chronic bronchial asthma and did not lead to a deterioration in pulmonary function.[295] In addition, in patients with chronic asthma, a single dose of azelastine 4mg resulted in rapid onset of bronchodilating activity with a 12-hour duration of action as demonstrated by a clinically and statistically significant mean percent improvement in forced expiratory volume in 1 second (FEV_1),[296] while the same dose of azelastine both improved their symptoms and reduced their requirement for adjunctive anti-asthma medication.[297]

Grant and coworkers[298] demonstrated that cetirizine significantly improved asthma symptoms in patients with seasonal allergic rhinitis and concomitant asthma, although cetirizine had no statistically significant effect on lung function as measured by peak flow or FEV_1. These findings are similar to those from a number of other studies.[299-301] Two randomised crossover studies of terfenadine and placebo reported improvements in symptoms and lung function in treated patients with atopic asthma.[302,303] In an uncontrolled study which looked at the effect of loratadine on 25 patients with allergic asthma, Kroll et al.[304] found that a dose of 10mg daily for 6 weeks was associated with improved pulmonary function, reduced asthma symptoms and reduced bronchodilator use. However, loratadine administered to 17 patients with perennial asthma failed to have an effect on symptoms or peak flow,[305] and when given as an adjunct to standard asthma therapy had little or no effect in a double-blind crossover study of 35 patients with moderate-to-severe asthma.[306] A more recent study using 193 patients compared the combined medication loratadine 5mg/pseudoephedrine 120mg versus placebo. Loratadine/pseudoephedrine was found to significantly improve pulmonary function and both rhinitis and asthma symptoms.[307]

These studies suggest that the second generation antihistamines are well-tolerated and efficacious as adjunct therapies in patients with asthma and concomitant rhinitis, dermatitis or urticaria. In particular, the link between the upper and lower respiratory airways is now well established[308] and this has provided an additional rational for the use of H_1 receptor antagonists in patients with both rhinitis and asthma.

One other consideration is that the documented anti-inflammatory effects of some of these drugs might be effective in preventing the progression from atopic dermatitis to allergic asthma in children, a process known as the 'allergic march'. A recent double-blind, randomised, placebo-controlled, multicentre trial evaluated the ability of cetirizine 0.5 mg/kg bodyweight to prevent the development of allergic asthma in over 800 at-risk children for a period of 18 months. Children were selected on the basis of a diagnosis of atopic dermatitis together with a parent or sibling history of atopic disease. Raised immunoglobulin (Ig)E levels and raised specific IgE to house dust mite, grass pollen or cat dander were found to be predictive of the development of asthma. In the subgroups of children sensitised to pollen or house dust mite, cetirizine treatment was found to halve the number of patients developing asthma. During this prolonged treatment period in young children and infants aged 1 to 2 years there was no higher incidence of adverse effects, including somnolence, in the cetirizine group (2.3%) compared with the placebo group (2.0%), with the exception of urticaria which was significantly less frequent in the cetirizine-treated group (5.8 *vs* 16.1% for the placebo group).[309] This study provides evidence that consideration should be given to cetirizine as a primary pharmacological intervention strategy to prevent the de-

velopment of asthma in specifically-sensitised high risk groups of infants.

5. Conclusions

In the light of the foregoing, what conclusions can we make with regard to the current classification of antihistamines into first or second generation drugs? It can be argued that the latter represents too large and indistinct a grouping since it was based primarily on the concept of separating sedating from nonsedating drugs. The group comprises compounds with a spectrum of antihistamine and anti-allergic properties, and includes drugs with proven cardiotoxic effects and others with the potential for adverse drug interactions. In terms of safety, cetirizine, fexofenadine and loratadine appear to be the most reliable, although a question mark does remain concerning the potential for cetirizine to cause a degree of somnolence in some individuals. However, all antihistamines possess this potential as a function of histaminergic mechanisms involved in the control of CNS arousal.[310] When pharmacokinetic properties are taken into account, cetirizine, fexofenadine and acrivastine are the only drugs which are not metabolised by the liver and which, to date, show no evidence of drug interactions. Thus, they can be given with confidence to patients who are in need of other treatment or who demonstrate hepatic impairment. Cetirizine has a remarkably low V_d and thus does not accumulate in lean tissues, and has by far the most well documented profile of anti-allergic effects. Importantly, it not only has potential as a useful adjunct therapy in patients with asthma who experience rhinitis, but documented evidence is also now available demonstrating its usefulness in preventing the development of asthma in at-risk children with atopy. In conclusion, it is too early to talk about a third generation grouping of antihistamines; however, future membership of such a classification could be based on a low V_d coupled with a lack of sedation effects, drug interactions and cardiotoxicity.

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