

Position paper

The clinical safety of H_1 -receptor antagonists

An EAACI position paper*

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Antihistamines, or H_1 -antagonists, despite their pronounced unwanted effects, were the first efficacious drugs to be used for the symptomatic relief of allergic diseases. In recent years, pharmacologic research has produced a new generation of antihistamines, the so-called *newer* or *second-generation* antihistamines, with high potency and minimal sedative effects as compared to the older or classical antihistamines. Recently, the newer antihistamines have become the focus of medical scientific interest for two reasons. Firstly, many of these drugs have been claimed to have additional antiallergic properties, and, secondly, there are several reports of possible cardiotoxic effects and carcinogenicity. In particular, the safety issue is of central importance because of the *widespread use* of antihistamines in current medical practice. Furthermore, since antihistamines are used to treat non-life-threatening disorders, their risk/benefit ratio must be carefully evaluated (1).

In this paper, we review the available data on the safety of the newer antihistamines and their risk/benefit ratios in order to provide helpful information for both specialists and general practitioners.

The histaminergic system

Histamine, originally identified by Henry Dale in 1910 (2), has been recognized since the 1920s as a major pathogenetic mediator of allergic disorders, such as hay fever, urticaria (3), and anaphylaxis. The exact mechanism of action remained unknown until 1966 when the histamine H_1 receptor was identified (4). This receptor is distributed widely on many tissues in the body, including smooth-muscle cells of the bronchial tree, the intestine, and the vasculature. The predominant features of H_1 -receptor stimulation are bronchoconstriction, spastic contraction of intestinal smooth muscle, and vasodilation. Knowledge of the histaminergic system has recently been extended by the discovery of the H_2 receptor (5), stimulation of which promotes gastric acid secretion, and the H_3 receptor (6), which is associated primarily with the central nervous system and whose functions are not completely clarified, although a selective antagonist (thiopramide) is now available.

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Antihistamines: general aspects

Classification

The pharmacologic class of antihistamines includes a large number of compounds with various pharmacokinetic-pharmacodynamic properties. A classification, although difficult to make, is therefore required. Various criteria have been proposed, including chemical structure, rapidity of onset of action, pharmacodynamic properties, etc. In practical terms, the most useful classification is that based on both H₁ selectivity and the absence of sedation. These criteria allow us to distinguish two main subclasses of H₁-receptor antagonists: the *first-generation* or *older* antihistamines and the *new* or *second-generation* or *non-sedating* antihistamines. Under this system, ketotifen and oxatamide differ from the remaining newer antihistamines in that they exert serotonergic and anticholinergic actions. Thus, these compounds should be more properly defined as "intermediate" antihistamines. Furthermore, the recent description of additional "antiallergic" properties for some of the new compounds has suggested a further possible subdivision of new antihistamines. A large number of data on this topic are available and need careful global revision. For this reason, the evaluation of the antiallergic effects of the new antihistamines will be the subject of a separate position statement.

First-generation antihistamines

The first H₁-receptor antagonists became commercially available in the 1940s (7) and were widely prescribed subsequently. However, this group of compounds, which includes chlorpheniramine, diphenhydramine, hydroxyzine, promethazine, pyrilamine, and triprolidine, has many troublesome side-effects. The most problematic effect, sedation, severely limits their clinical use and may result in suspension of therapy. The sedative effect of older compounds is a consequence of their lipid solubility, which allows penetration of the blood-brain barrier (8). Furthermore, the older molecules, because of their poor receptor selectivity (9), also exert some blockade of muscarinic cholinergic, α -adrenergic, and tryptaminergic receptors, a fact which may partially explain the additional adverse effects observed in clinical practice, such as constipation, difficult urination, xerostomia, cough, nausea, and vomiting. The effects on other receptors may also contribute to their observed sedative effects. Furthermore, the older antihistamines have a short half-life, necessitating multiple daily dosing to maintain satisfactory H₁ blockade. The older antihistamines are no longer in routine use for the

treatment of allergic disorders, at least in Europe. Only hydroxyzine, because of its marked antipruritic and mildly sedative effect, is still used to treat chronic urticaria and atopic dermatitis. However, the older antihistamines (particularly chlorpheniramine) retain some importance as sedative or antipsychotic drugs and are used intravenously, after epinephrine, in the emergency treatment of anaphylaxis. Finally, the capacity of the older antihistamines to counter motion sickness, probably because of their central antimuscarinic actions, can also be advantageous.

Second-generation antihistamines

The commercially available newer antihistamines include acrivastine, astemizole, azelastine, cetirizine, ebastine, levocabastine, loratadine, ketotifen, oxatamide, and terfenadine. For these molecules, a large number of clinical trials and experimental data are available in the literature. In addition, some other new molecules, including emedastine, epinastine, mizolastine, noberastine, and setastine, are currently undergoing clinical trials (10).

The newer antihistamines have higher affinity for H₁ receptors than the older ones and almost negligible affinity for other amine receptors. In addition, these molecules are relatively large, have long side-chains, and are poorly soluble in lipid. Therefore, the blood-brain barrier penetration, the sedative effects, and the additive effects with alcohol are also reduced. Another possible reason for the limited sedative effects of the newer antihistamines is their selectivity for the peripheral, rather than the central, H₁ receptors, although the existence of differences between these receptors is still a matter of debate (11, 12).

The effects of the binding of the new antihistamines to the H₁ receptor are not readily reversible by simple washout of the antagonist. The half-lives of the new antihistamines are quite variable, ranging from 2 h for acrivastine to 9.5 days for demethyl-astemizole, the active metabolite of astemizole (13, 14). Furthermore, the pharmacodynamics of H₁ blockade is not directly predictable from a knowledge of the metabolic half-life of a drug. In fact, the tissue distribution, the generation of active metabolites, and the poor reversibility of receptor binding, prolong their clinical effects, e.g., inhibition of the wheal and flare reaction in the skin, independently of their serum concentrations.

For example, terfenadine (60–120 mg) rapidly suppresses the wheal and flare reaction (15), an effect which persists for at least 24 h (16). A single dose of astemizole is not completely effective in suppressing the wheal and flare reaction (17, 18),

while a long period of treatment results in potent and long-lasting inhibition of the cutaneous reaction (14, 19). For this reason, astemizole is indicated for long-term treatments, but not for prompt relief of symptoms. The suppression of the wheal and flare response by a single dose of loratadine (10 mg) is demonstrable within 1 h (20) and lasts 12–24 h (12, 20, 21). Administered as a single dose, cetirizine (10 mg) causes prompt suppression (within 1 h) of the wheal and flare response, lasting up to 24 h (22, 23). The wheal and flare suppression after azelastine administration is dose dependent, peaking at about 4 h and lasting up to 1 week after a short course of treatment (24). With levocabastine, which has been developed for topical administration only, peak plasma levels are attained 2 h after nasal administration, and steady state is reached in 7–10 days (25).

Almost all these compounds are largely metabolized by the liver (12), some of them producing active metabolites. Examples include a carboxylic acid derivative from terfenadine, demethylastemizole from astemizole, carboethoxy-loratadine from loratadine, and demethyl-azelastine from azelastine. An exception to this is cetirizine, which is poorly metabolized and largely excreted unmodified in the urine (26). Whereas loratadine is metabolized in the liver and excreted in feces, the metabolite of loratadine is excreted in the urine. This leads to an equivalent renal and hepatic clearance of this drug (27).

Sedative effects of antihistamines

The pharmacokinetic properties of the second-generation antihistamines, including poor lipid solubility, selectivity for H_1 receptors, and negligible crossing of the blood-brain barrier, partially explain their reduced sedative effects (28). The term "sedation" describes a wide range of subjective experiences and can mean drowsiness, increasing likelihood of falling asleep, loss of alertness, decreased concentration, and, in more medical terms, global reduction of psychomotor performance. In this regard, the histaminergic system has

been clearly demonstrated to affect alertness, vigilance, and slow-wave activity on the electroencephalogram (EEG) during sleep (29).

The problem of sedation is of great importance for the safety of workers and drivers (30) and for the school performance of children. Thus, the widespread use of these drugs requires *rigorous scientific assessment and measurement* of any untoward sedative effects. This can be done by both clinical and instrumental tests (31, 32), the most common of which are driving tests (both actual and simulated), psychomotor tests, the Stanford auto-evaluation scale for sleepiness, the EEG, and acoustic evoked potentials (Table 1). Driving tests, because of their simple execution and the possibility of using driving simulators, are particularly suitable for the global evaluation of psychomotor performance (33); therefore, they have been widely used in the reported studies. Each of the several psychomotor tests investigates predominantly one particular aspect of performance such as coordination, reaction time, memory, alertness, etc. A rigorous, double-blind study of the potential sedative effects of antihistamines should be conducted in healthy volunteers, possibly with comparison with a sedative antihistamine or evaluation of possible additive effects with alcohol. A remarkable number of well-conducted trials on healthy volunteers have demonstrated reduced sedative effects of the newer antihistamines compared with first-generation drugs.

Dhorrnanitra et al. (34) demonstrated the absence of sedation with astemizole using driving tests, while similar results were obtained by Hindmarch & Bhatti (35) in comparing astemizole and chlorpheniramine with and without alcohol. Bate-man et al. (36) confirmed the lack of effect of astemizole on ethanol metabolism. In 85 subjects, Moser et al. (37) demonstrated that astemizole (30 mg) did not impair responses in psychomotor and subjective assessment tests, while significant sedation was obtained with ketotifen (1 mg). Moreover, astemizole, 30 mg q.i.d. for 7 days, did not affect the oculovestibular reflex in 20 subjects evaluated in a double-blind study (38).

Table 1 Tests evaluating sedation

Driving tests	Psychomotor	Subjective	Instrumental
Actual, driving on driving simulator, weaving, steering, gate acceptance, brake reaction time	Memory, mental arithmetic, auditory vigilance, Glass-bead picking	Stanford scale for sleepiness, Visual analog scale	Continuous EEG, P300 latency
Driving simulator	Critical tracking, Card sorting, Digit-symbol substitution		Multiple latency, Flicker fusion, Vestibular-ocular reflex

Terfenadine has been reported to have significant sedative effects only at 240 mg, while at a dose of 120 mg it did not affect driving or psychomotor performance (39). In a study in 20 volunteers (40), terfenadine (120 mg for 3 days) did not affect psychomotor tests or reaction time. Similar results were obtained with different psychomotor tests after giving single doses of terfenadine of 60 mg (41) and 120 mg (42). Goetz et al. (43) demonstrated the absence of sedation with terfenadine, 60 mg b.i.d., in a subchronic treatment study. The absence of sedation in healthy volunteers was also demonstrated for terfenadine by the evaluation of evoked acoustic potentials (44) and in a multiple sleep latency test (45). Finally, terfenadine, 120 mg q.d. for 7 days, did not affect EEG parameters (46). Loratadine, given in single doses of 10 and 20 mg (47) and in multiple doses (48), did not show any significant sedative effects when evaluated by driving tests or psychomotor tests (49). Loratadine in a single 20-mg dose neither modified psychomotor performance nor caused a subjective sedation (50). Furthermore, loratadine impaired the visual-motor performances of healthy subjects (51) at a dose of 40, but not 20 or 10, mg q.d., while a single 10-mg dose did not affect flying simulator performance in 40 healthy subjects (52). Finally, a single 10-mg dose of loratadine did not affect driving performance and the EEG recorded during driving (53).

As for cetirizine, in two placebo-controlled studies, Gengo et al. demonstrated that 5, 10, and 20 mg did not impair psychomotor and driving performance as compared to 25 mg hydroxyzine (54) or diphenhydramine 50 mg (55). A study performed on 60 healthy volunteers (56) with psychomotor and driving tests showed the absence of sedative effect of cetirizine in doses of 5, 10, and 20 mg. In a study evaluating driving performances, memory, and sleep latency in 27 healthy volunteers, cetirizine 10 mg q.d. or terfenadine 120 mg q.d. for 4 days did not affect the test results (57). Tripolidine was used as positive control. Moreover, no difference was found between cetirizine and placebo with a visual analog scale either in a subchronic study (58) or with a single dose of 10 mg (59). The safety of a single 10-mg dose of cetirizine was confirmed in a further study investigating P300 latency (60). On the other hand, in a clinical study of cetirizine efficacy (61) in allergic rhinitis, a significant incidence of mild to moderate sedation was reported with 10- and 20-mg doses. Finally, in a study by Ramaekers et al. (53), a single 10-mg dose of cetirizine appeared to affect significantly actual driving performance, even though the authors themselves did not consider the effect to be of clinical relevance.

Topical administration of levocabastine to the eye or nose did not cause significant sedation in

either subchronic (62) or single-dose (63) studies. Similar results were found with topical azelastine (64). Oral acrivastine at single doses of 4, 8, and 16 mg did not affect psychomotor tests (65) when compared with a positive control (tripolidine). Single doses of 10 and 50 mg of ebastine did not affect psychomotor performance, but the 50-mg dose caused a significant subjective sedation (66). Finally, ebastine, administered orally at 10, 20, or 30 mg for 5 days, did not impair driving performance in contrast to triprolidine 10 mg (67).

Arrhythmic effect

Recently, there have been several reports that therapy with some of the newer antihistamines may be associated with cardiotoxicity, particularly prolongation of the Q-T interval and precipitation of the potentially life-threatening condition of torsade de pointes. While the histaminergic system may exert a small, but significant, effect on cardiac electric activity (68), it is unlikely that blockade of this by antihistamines is responsible for the reported cardiotoxicity, as the effect is unrelated to H₁-receptor blocking activity. Rather, the effect appears to be related to the particular chemical structure of some drugs. To appreciate this, one must realize that the antihistamines have evolved from the same basic chemical structure as local anesthetics, antipsychotics, β -adrenoceptor blockers, and some calcium-channel blockers. Several members of this group – for example, haloperidol and sotalol – have the capacity to reduce the magnitude of outward repolarizing K⁺ currents, enhance inward depolarizing Na⁺ or Ca²⁺ currents, or both, thereby triggering the development of early depolarizations that initiate the cardiac abnormalities. Thus, it is hardly surprising that some of the more complex antihistamine molecules also have the potential to exert such effects.

In 1968, Lauria et al. (69) investigated the possible effects of hydroxyzine on the cardio-vascular system of elderly subjects, following a previous experimental study showing a hypotensive effect (70), but found no significant effect. In 1975, Hollister (71) reported electrocardiographic alterations, particularly T-wave lowering and flattening together with prolongation of the Q-T interval (although without correction for rate), in patients treated with hydroxyzine. It is of note that this study was performed in elderly people receiving huge doses of the drug, 300 mg daily for 9 days. Further reports (Table 2) on the cardiac adverse effects of antihistamines appeared sporadically (72–75), and the problem remained of limited interest in subsequent years, until new reports appeared on the arrhythmic effects of the newer antihistamines.

Table 2 Reported cardiac adverse effects of older antihistamines

Drug	Patient no.	Event	Note	Author(s)	Reference
Hydroxyzine	9	None (sedation)	50–57 mg	Lauria et al.	69
Hydroxyzine	27	ECG abnormality	300 mg	Hollister	71
Pheniramine	1	Ventricular arrhythmia, torsade de pointes	Oral dose unknown; plasma: 10 µg/ml	Bobik & McLean	72
Hydroxyzine	1	Tachycardia	25 mg	Magera et al.	73
Cyproheptadine	1	Torsade de pointes, death	32 mg	Bojuu et al.	74
Pyrimamine	1	Cardiogenic shock	> 10 g	Freedberg et al.	75

In 1986, Craft (76) reported a case of prolonged Q-T interval and torsade de pointes in a patient after an overdose of astemizole (200 mg). In 1988, two further reports (77, 78) of ventricular tachyarrhythmia, one with a normal dose and another with a high dose of astemizole, appeared, and, in 1989, Bishop & Gaudry (79) described a prolonged Q-T interval after astemizole overdose. During the same period, several reports of ventricular arrhythmia appeared also for terfenadine. Davies et al. (80) and McConnel & Stanner (81) reported ventricular dysrhythmia after overdose of terfenadine, while Monahan et al. described an episode of torsade de pointes with a recommended therapeutic dose of terfenadine in association with ketoconazole and cefaclor (82). Tobin et al. (83) reported prolonged Q-T interval in a case of accidental poisoning with astemizole (100 mg), and Hoppu et al. (84) reported prolonged Q-T interval and torsade de pointes in six children who had consumed high doses of astemizole, about 12-fold higher than those recommended. Clark & Love (85) also reported a case of Mobitz-type 2 heart block with torsade de pointes after astemizole overdose (250 mg). In two further case reports, Q-T prolongation and torsade de pointes were described with astemizole, but one of the patients presented Romano-Ward syndrome, a congenital prolonged Q-T interval (86), and the other had a previous prolonged Q-T interval and mitral prolapse (87). In a patient with liver cirrhosis, the administration of 240 mg of terfenadine caused prolongation of the Q-T interval and ventricular ectopic beats (88). Saviuc et al. (89) reported a case of prolonged Q-T interval and torsade de pointes after astemizole poisoning (200 mg) together with hydroxyzine and ethanol consumption. Similar arrhythmogenic effects, namely, prolonged Q-T interval, ventricular bigeminy, and A-V block, were described in five children after relatively high doses of astemizole (90). Finally, Good et al. (91) recently reported a case of ventricular tachycardia with prolonged Q-T interval after loratadine in a patient suffering from ischemic coronary disease and coadministration of quinidine.

As summarized in Table 3, in almost all of the cases reported in the literature, an overdose of the drug was present: i.e., consumption exceeded that recommended by the manufacturer. However, in several cases, impaired liver function or the concurrent use of drugs which interfered with the activity of the liver enzyme cytochrome P450 was associated with cardiotoxicity (92). As almost all of the newer antihistamines undergo hepatic metabolism via the cytochrome P450 system, compromised liver function may result in accumulation of the parent drug, which, if it has quinidine-like effects, may result in unwanted cardiac effects. The impairment by erythromycin and ketoconazole of the metabolism of terfenadine with subsequent drug accumulation and adverse effects on cardiac depolarization has been confirmed by Honig (93) and Eller (94). Two cases of possible interaction between itraconazole and terfenadine, with subsequent torsade de pointes (95) and ventricular fibrillation (96), have also been reported. These findings have been confirmed by Zimmermann et al. (97) and Moore et al. (98). Furthermore, van Peer et al. (99) demonstrated that ketoconazole also inhibits loratadine metabolism. It is of note that the possible interference by the macrolides on drug metabolism has been recognized since the work of Pessayre in 1983 (100). Using a guinea pig model to study the effects of antihistamines on cardiac rhythm, Hey et al. demonstrated that intravenous terfenadine, astemizole, and ebastine induced significant arrhythmogenic effects which were enhanced by ketoconazole, while cetirizine, carbastine, and norastemizole appeared to be devoid of cardiac effects (101, 102). Cetirizine and acrivastine are excreted with no metabolism and, together with loratadine which is about 40% excreted in the urine (26, 27), therefore appear to be the least likely to be arrhythmogenic.

On the other hand, several studies have demonstrated the safety of the antihistamines mentioned in healthy subjects in the absence of macrolide antibiotic or ketoconazole therapy. Warin (103) reported no ECG abnormalities in 12 subjects consuming 120–360 mg terfenadine, while Offenloch

Table 3 Reported cardiac adverse effect of new antihistamines

Drug	Patient no.	Event	Note	Author(s)	Reference
Astemizole	1	TDP	200 mg*	Craft	76
Astemizole	1	TDP	20 mg	Snook et al.	77
Astemizole	1	TDP	10 mg	Simons et al.	78
Astemizole	1	prol. Q-T	250 mg*	Bishop & Gaudry	79
Terfenadine	4	prol. Q-T	Plus ibuprophen	Davies et al.	80
Terfenadine	1	TDP	Plus ketoconazole	Monahan et al.	82
Terfenadine	1	TDP, cardiac arrest	360 mg/day*	McConnel & Stanner	81
Astemizole	1	prol. Q-T	100 mg*	Tobin et al.	83
Astemizole	6	TDP, bradycardia	20–200 mg*	Hoppu et al.	84
Astemizole	1	prol. Q-T, TDP	250 mg*	Clark & Love	85
Terfenadine	8	prol. Q-T, TDP	Plus erythromycin	Honig et al.	93
Terfenadine	1	TDP	Plus ketoconazole	Zimmermann et al.	97
Terfenadine	5	TDP, syncope	Plus ketoconazole/josamycin	Moore et al.	98
Terfenadine	1	TDP	120 mg plus itraconazole	Polyola-Sintonen et al.	95
Astemizole	1	TDP, prol. Q-T	Congenital prol. Q-T	Broadhurst & Nathan	86
Astemizole	1	TDP	Previous prol. Q-T	Sakemi & van Natta	87
Terfenadine	1	TDP, syncope	Plus itraconazole	Crane & Smith	96
Astemizole	1	TDP, prol. Q-T	200 mg*	Savuc et al.	89
Astemizole	5	A-V block, bradycardia	2–12 mg/kg	Wiley et al.	90
Loratadine	1	Tachycardia, prol. Q-T	Plus quinidine	Good et al.	91

TDP = torsade de pointes; *prol. = prolonged; *overdose.

& Kahner (104) demonstrated the safety of terfenadine in a study involving 10 volunteers. In two recent studies conducted in healthy volunteers, loratadine (40 mg q.i.d.) (105), cetirizine (20–60 mg q.i.d.) (106), and acrivastine (107) have been shown not to affect the Q-Tc. Finally, to date, there are no case reports of adverse cardiac effects by acrivastine, azelastine, cetirizine, or ketotifen.

Apart from the specific contraindications cited, the incidence of cardiotoxic adverse effects appears to be negligible in view of the widespread use of antihistamines (108). Furthermore, it should be re-emphasized that cardiotoxicity is almost invariably associated with high circulating levels of the parent form of a small number of antihistamines (often prodrugs) that are metabolized by the liver to agents with potent H₁-blocking activity but which do not exert cardiac effects.

Carcinogenicity

A recent experimental study on mice by Brandes et al. (109) proposed a possible carcinogenic effect of some antihistamines. It is of note that the same authors previously reported similar results with the antidepressant drugs fluoxetine and amitriptyline (110). Briefly, a population of mice with induced melanoma or fibrosarcoma were given intraperitoneal doses of astemizole, loratadine, hydroxyzine, doxylamine, or cetirizine in doses comparable to those given in clinical practice. After 21 days, the wet weights of the tumors were

assessed and compared to those of control groups. An increase of the tumor growth was greatest for astemizole and loratadine, followed by hydroxyzine, while doxylamine and cetirizine were comparable to placebo. However, the results obtained in rodents are not immediately transferable to man, because of both the different experimental conditions used and the differences in cellular metabolic systems (111). Finally, the results obtained by Brandes et al. were not reproduced in subsequent studies (112). These results, although interesting from a speculative viewpoint, are not consistent with clinical experience, as no report of carcinogenicity has been published during more than 50 years of clinical trials and clinical use of antihistamines. Furthermore, no link between antihistamine treatment and carcinogenicity has ever been suspected. Indeed, surveying these results, the US Food and Drug Administration (FDA) concluded that the cost/benefit ratio and the clinical use of antihistamines should not be modified (113).

Conclusions

With respect to efficacy and nonsedation, the newer antihistamines show a very favorable risk/benefit ratio. Their efficacy in the treatment of perennial and seasonal allergic rhinoconjunctivitis and of urticaria has been clearly demonstrated in the literature and is supported by long clinical experience (27, 114–116). Thus, these clinical conditions represent the ideal indications for the use

of the newer antihistamines. The best-known and most troublesome side-effect, sedation, appears to be largely avoidable with the second-generation antihistamines, as reviewed by Hindmarch (117) and O'Hanlon & Ramaekers (118), when prescribed at the recommended doses. Thus, long-term treatment is both safe and recommended.

The possible, but extremely rare, cardiotoxic effects appear to be related, in most cases, to an overdose or reduced hepatic metabolism of certain drugs, with abnormal accumulation and consequent effect on cardiac repolarization. The arrhythmogenic effects can be avoided if simple but important rules are followed (119):

- Do not exceed the dose prescribed by the manufacturer: an increased plasma concentration does not necessarily improve the clinical efficacy, but does increase the risk of drug accumulation.
- Avoid the concurrent administration of drugs which are known to interfere with the hepatic metabolism of antihistamines: e.g., azolic antifungal drugs such as ketoconazole or macrolide antibiotics such as erythromycin.
- Particular care must be taken when administering antihistamines to subjects with significant impairment of liver function or to subjects with significant risk of cardiac rhythm disturbance, particularly prolonged Q-T interval or A-V block.
- In patients at risk of cardiac rhythm disturbance, choose antihistamines which do not have quinidine-like actions and which are not metabolized via the cytochrome P450 pathway.

In conclusion, the newer antihistamines appear to be useful and relatively safe drugs, but require, like all drugs, careful case-by-case evaluation in order to recognize the possible contraindications.

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