



Update

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Nonsedating Antihistamines

Concerned about a risk of cardiotoxicity, physicians have begun to evaluate the role of nonsedating antihistamines in treating allergic disorders.

The concern reached new heights last year following a reported lethal cardiac arrhythmia in a patient taking terfenadine (Seldane) and the antifungal agent ketoconazole (Nizoral). The latter drug can impede terfenadine metabolism via the liver, resulting in elevated blood levels of the antihistamine.

Following the death, an investigation by the Food and Drug Administration uncovered several other deaths that appeared related to terfenadine therapy. In July the FDA ordered Marion Merrell Dow to strengthen the cautionary language on terfenadine labeling. The new order upgrades precautions about using the antihistamine to the status of contraindication.

Both terfenadine and astemizole (Hismanal), the only other non-sedating antihistamine on the market, have well-documented cardiotoxicity risks, dating back at least to the mid-1980s (Simons and

Overdose and drug interaction with ketoconazole or erythromycin have been associated with cardiotoxic reactions.

Simons, *Annals of Allergy* 1991, Vol. 66, p. 5).

"The risk of cardiotoxicity is not a new finding," said Harold Nelson, M.D. "The risk has been known for some time, but clearly, the early reports of cardiac arrhythmias did not get enough attention because additional patients have died from apparent drug interactions."

Cardiac arrhythmias associated with the nonsedating antihistamines appear to arise from prolongation of the Q-T interval. The major risk appears to involve progression to torsade de pointes, which in turn can lead to syncope and cardiac arrest (Craft, *Br Med J* 1986, Vol. 292, p. 660; Simons et al, *Lancet* 1988, Vol. 2, p. 624).

A history of or predisposition for cardiac problems does not seem to

play a role in the arrhythmia risk. As an example, Dr. Nelson cited the case of a young Los Angeles woman who had athlete's foot, treated with ketoconazole, as her only identifiable medical condition prior to an antihistamine-associated arrhythmia.

Initially, the risk of cardiac arrhythmias appeared limited to overdose, particularly with respect to astemizole.

"Physicians used to be taught that, since astemizole is long acting but takes a while to build up, loading doses should be used," said Dr. Nelson. "That's no longer the case and in view of present knowledge would be totally inappropriate.

"The key to reducing or eliminating the risk of cardiac arrhythmias, especially with astemizole, is to make sure patients take no more than the recommended amount, even if symptoms aren't relieved. Astemizole or terfenadine could easily be taken in excess because neither drug is sedating."

More recently, clinical evidence has revealed a risk of terfenadine interaction with ketoconazole and with erythromycin, which also

Nasal steroids are effective against congestion, while antihistamines appear to work better for ocular symptoms.

blocks the antihistamine's metabolic pathway through the liver. In addition, patients with impaired liver function face an increased risk of cardiotoxicity when taking terfenadine, and possibly astemizole.

"With terfenadine the key is to warn patients about possible drug interactions," said Dr. Nelson.

"[Ketoconazole and erythromycin] are drugs that could be prescribed by a different physician treating a separate problem, and the possibility that the patient is taking terfenadine might not even be considered."

Janssen also has revised astemizole package inserts to contraindicate use of the drug in patients who are taking erythromycin, ketoconazole, or itraconazole, an anti-fungal structurally similar to ketoconazole. The action came late last year following reports of two cases of cardiac arrhythmia possibly related to drug interaction involving astemizole used in conjunction with erythromycin or erythromycin and ketoconazole.

Beyond creating concern, the cardiotoxicity issue has provided a backdrop for reviewing the therapeutic options for allergic disorders. A number of efficacy and economic issues warrant careful physician consideration.

As a drug class, antihistamines — whether sedating or nonsedating — have no effect on nasal obstruction. Because of that limitation, the drugs should not be used by themselves when symptomatology includes congestion. Dr. Nelson favors topical steroids for patients who have nasal obstruction.

"In head-to-head clinical comparisons with antihistamines, nasal steroids generally have shown significantly greater benefit," he

said. "Nasal steroids are very effective against nasal obstruction, and they are fairly effective at relieving other symptoms that typically respond to antihistamines — sneezing, itchy nose, rhinorrhea. Intranasal steroids are least effective for ocular symptoms.

"Antihistamines are particularly beneficial for ocular symptoms. In fact, that is the one area in which antihistamines have a clear advantage over topical steroids."

Package labeling of conventional antihistamines states the drugs should not be used by asthmatics. Dr. Nelson said the warning is based on the presumption that the anticholinergic properties of these older antihistamines would decrease secretions and cause mucus plugging in the chest. Despite a lack of clinical evidence to support the hypothesis, the FDA has failed to eliminate the label warning, he said.

A conventional antihistamine combined with a decongestant offers another alternative for patients with nasal obstruction. Many of these combination preparations are available over the counter in 12-hour tablets and capsules. They also come in generic formulations.

If nasal obstruction is the predominant symptom, a simple oral decongestant, such as pseudoephedrine, might be appropriate. These drugs come in a variety of generic and over-the-counter formulations.

Therapeutic options also include nasal cromolyn sodium and topical ipratropium bromide, neither of which appears to have more than a limited clinical role, according to Dr. Nelson.

"There is no question that cromolyn works, but it works less well than topical steroids," he said. "More importantly, cromolyn has to



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be administered four to six times a day, whereas steroids can be used just twice a day.

Ocular cromolyn, on the other hand, probably is the safest and most effective chronic therapy for severe allergic conjunctivitis.

"It has to be given fairly often," Dr. Nelson noted, "but it's probably the best treatment for really bad conjunctivitis. If the conjunctivitis is only intermittent, then I recommend some type of vasoconstrictor eyedrops."

As for topical ipratropium, he commented, "It has been shown to be useful against rhinorrhea, which usually responds adequately to other treatments. It has not been shown to be effective for postnasal drainage and obstruction, which are oftentimes the most troublesome symptoms."

Nasal washes may help reduce obstruction in some patients, especially as an antecedent to topical steroids.

The rationale behind the washes is to clear out mucus and allow nasal steroids to gain access to the mucosa," said Dr. Nelson. "We know that cells and mediators, as well as allergens, pollutants, and other irritants, build up in nasal secretions. As a result, there may be some benefit to periodic washings. Probably the patients who benefit most are those who have thick nasal secretions, as opposed to patients who have acute allergic rhinitis."

The nature of the symptoms — chronic or episodic — also should figure into the therapeutic choice. For patients who have fairly well identified periods of continuous symptoms, Dr. Nelson again recommends nasal steroids. In general, antihistamines are more appropriate for intermittent symptoms; astemizole represents the notable exception.

"Though Hismanal can have some effect fairly quickly, there is no question that it usually takes time to build up to maximal effect," said Dr. Nelson. "Once the drug reaches maximal effect, it takes a long time



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to wear off. For those reasons, astemizole is better suited for treating chronic symptoms. Terfenadine and most conventional antihistamines are better choices for episodic or intermittent symptoms."

On the surface, the sedation issue seems fairly straightforward. In fact, several considerations can figure into the selection of a drug. Unquestionably, conventional antihistamines, across the board, have the ability to induce sedation and drowsiness. However, just as clearly, patients may be affected to varying degrees by the sedative properties. Some patients may report little or no sedation. Clinical experience also may guide physicians to fairly clearcut distinctions among the antihistamines.

The development of antihistamine-decongestant combinations has added another element to

Antihistamine-decongestant combinations appear to have the same CNS effects as non-sedating antihistamines.

the sedation discussion. The stimulatory effects of the decongestant tend to offset the antihistamine's sedative properties. The net impact on central nervous function compares favorably with that of the nonsedating antihistamines.

Marion Merrell Dow recently introduced a Seldane formulation that includes a decongestant. Physicians might already have heard complaints about sleep disturbances from some patients.

"You have no sedation from the antihistamine and therefore an

Some sedation may be desirable for patients who have itching due to eczema or urticaria.

unopposed stimulatory effect of the decongestant." noted Dr. Nelson. "Not surprisingly, there have been problems with insomnia."

In general, drowsiness is an unwanted effect of treatment with conventional antihistamines. However, some degree of sedation might prove beneficial in certain patients who have particularly bothersome itching due to eczema or urticaria, Dr. Nelson observed.

With respect to cost, the non-sedating antihistamines and the nasal steroids generally rank as the most expensive drug therapies for allergic disorders.

"Given the comparable cost, I usually recommend nasal steroids because of what I see as the steroids' clearcut advantages in effectiveness," said Dr. Nelson. "Topical steroids cause no major side effects. Nasal bleeding is the only possible problem of consequence. Most patients with allergic rhinitis tend to have nasal bleeding anyway, so it's difficult to say that the bleeding is caused by the steroids, although the bleeding probably is increased to some extent by steroids."

Conventional antihistamines tend to be the least expensive, especially when purchased in generic form, though the cost can vary considerably among drugs. Antihistamine-decongestant combinations usually cost somewhat more but still less than terfenadine, astemizole and nasal steroids.

On the horizon, several other non-sedating antihistamines are in various stages of clinical investigation. At this point, loratadine and cetirizine appear closest to winning FDA approval.

Clinical studies have yet to reveal any substantial differences between the investigational non-sedating agents and the two products current-

ly available.

"Compared to astemizole, both loratadine and cetirizine are fast acting, like terfenadine," said Dr. Nelson. "My sense right now is that cetirizine and loratadine probably will be suitable for intermittent use."

Sedation

Sedation occurs as a side effect of all first-generation antihistamines. Certain drugs and drug classes have earned clinical reputations for causing more or less sedation. In actuality, the degree of sedation experienced by an individual patient cannot be predicted by drug class.

"Most published information reflects the results of large clinical studies involving hundreds or thousands of patients. Often, very small differences are used to make the argument that one particular class of antihistamine is better or worse than another," said Lanny Rosenwasser, M.D.

"In reality, treatment becomes a trial-and-error situation much of the time. There are five or six drugs in every antihistamine class, and physicians have to look for the best

combination of efficacy and side effects in any one patient."

Further complicating the decision-making process, patient response varies widely within drug classes and for specific drugs.

"Frequently, the response can't be predicted; there is a huge scatter among patients," said Rosenwasser. "A particular drug from the ethanolamine class, for example, might be more sedating than other drugs in the class. But the drug might not cause much sedation in one patient, while the effect is accentuated in another."

The best analogy comes from use of anti-inflammatory drugs, Rosenwasser continued. Arthritis patients, in particular, have a well-documented variability in response to and tolerance of anti-inflammatory drugs.

"It's impossible to predict how a patient will react to a particular drug, despite some general caveats about some of the nonsteroidal anti-inflammatories," he said.

With the introduction of second-generation (non-sedating) antihistamines, patients' tolerance to

From the "Center Bibliography"

(citations courtesy of the Medical Library at National Jewish Center for Immunology and Respiratory Medicine)

The following citations were retrieved from the monthly Index Medicus. The articles can be accessed from your own medical library.

Heifets LB, Lindholm-Levy PJ, Comstock RD. Bacteriostatic and bactericidal activities of gentamicin alone and in combination with clarithromycin against *Mycobacterium avium*. *Antimicrob Agents Chemother* Aug 1992 36 (8) p1695-8 AN: 93037291

Bock SA. The incidence of severe adverse reactions to food in Colorado. *J Allergy Clin Immunol* Oct 1992 90 (4 Pt 1) p 683-5 AN: 93017550

Rosenwasser LJ, Joseph BZ. Immuno-hematologic diseases. *JAMA* Nov 25 1992 268 (20) p2940-5 AN: 93059940

Szefler S, Kamada AK, Hughes D, Brenner AM, Gelfand EW. Alternative treatments for asthma: assessing the need. *J Asthma* 1992 29 (2) p191-7 AN: 92348325

Berning SE, Huitt GA, Iseman MD, Peloquin, CA. Malabsorption of antituberculosis medications by a patient with AIDS letter. *N Engl J Med* Dec 17, 1992 327 (25) p1817-8. AN: 93063143

Leung DY. Immunopathology of atopic dermatitis. *Springer Semin Immunopathol (Germany)* 1992. 13 (3-4) p427-40. AN: 93031201

“Physical Illness, Psychologic Development and How the Twain Shall Meet”

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The Interplay of Chronic Illness and Adolescent Development: Longitudinal Views Stuart Hauser, MD, PhD

The Impact of Medical-Risk Status and Chronic Illness on Attachment Robert Harmon, MD

Childhood Chronic Illness and Families: Identifying Strengths, Understanding and Addressing Vulnerabilities Anne Kazak, PhD

Advanced Techniques of Family Therapy for Somatic Illness James Griffith, MD & Melissa Griffith, MSN

Psychosocial Interventions in Chronically Medically Ill: Models for Outcome Research Junius Gonzales, MD

Workshops

Medical Procedures as Precipitants of Post Traumatic Stress Disorder Thomas Roesler, MD

Use of Multi-family Groups with Medically Ill Children Marianne Wamboldt, MD

Methodologic Concerns for Inclusion of Biologic and Psychologic Measures in Clinical Research Stuart Hauser, MD, PhD

medication improved. However, efficacy has become more of an issue, said Rosenwasser, as some evidence suggests terfenadine in particular may not control symptoms as well as the older drugs do.

Ultimately, physicians should choose an antihistamine on the basis of clinical experience and individual patient profiles.

“Get an idea of how sick the patient is, how often the drug will need to be taken, and other pertinent factors. Then choose a drug,” said Rosenwasser. “If it works, if it’s well tolerated, fine. If not, then do some more clinical evaluation and pick

another drug. A large percentage of patients will have to try more than one drug.”

Unfortunately, the physician-patient communication loop frequently breaks when patients medicate themselves with over-the-counter antihistamines. Side effects, overuse, misuse, tolerance and other potential problems can be exacerbated as patients wend their own trial-and-error process. Rosenwasser encourages physicians to ask patients about OTC drug use whenever the opportunity presents, so some clinical guidance might be introduced to selection and use of

nonprescription antihistamines.

Occasionally, some degree of sedation might be desirable, usually when symptoms, such as urticaria-induced itching, interrupt or prevent sleep. In those cases, physicians might recommend an antihistamine perceived to cause more sedation than others. Additionally, patients might be advised to take the drug at night to further enhance the possibility of a good night’s sleep, said Rosenwasser.

Research

Two new antihistamines have shown promise in studies conducted at the National Jewish Center for Immunology and Respiratory Medicine.

Ebastine, a non-sedating antihistamine developed by Rhône-Poulenc Rorer, appears effective as one-a-day therapy for allergic rhinitis. In a trial at National Jewish, skin test reactivity to histamine was suppressed by up to 80% by a single dose of Ebastine, for up to 24 hours. A single morning dose of Ebastine also appeared effective for 24 hours in a study of children during the ragweed season.

Levocabastine, developed by Janssen Pharmaceuticals, yielded encouraging results against allergic rhinitis. Used twice daily in nasal spray form, the drug showed efficacy in a study during the weed pollen season. Levocabastine is extremely potent but has not been used systematically because it does cause sedation. Additional studies are planned at National Jewish.

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