

Side effects of rhinitis medications

Donald W. Aaronson, MD *Chicago, Ill.*

It is well known that the prevalence of allergic rhinitis and sinus disease is very high. The great majority of people with these conditions are treated with antihistamines and/or decongestants as the first line of therapy. In addition, many more people take readily available over-the-counter antihistamines at the first sign of an upper respiratory infection, even though these drugs are not effective for this condition. If oral drug therapy is insufficient to relieve and/or prevent the nasal/sinus symptoms of allergic rhinitis, the next line of therapy is topical, consisting either of cromolyn sodium or nasal steroids. None of these drugs is completely free of side effects, and this article will examine the more important side effects of each of these drug categories. In 1988, there were 48-million prescriptions written for antihistamines or antihistamine/decongestant combinations, and total antihistamine sales that year were almost 2-billion dollars.¹

Juniper and Guyatt, using a rhinitis quality-of-life questionnaire, found a variety of negative central nervous system (CNS) symptoms, including irritability, frustration, restlessness, fatigue, reduced productivity, and poor concentration associated with substantial upper respiratory disease due to allergens.² A recent study by Marshall et al., comparing several function measures before and during the allergy season, demonstrated significant impairment in verbal learning, decision-making speed, and psychomotor speed on both simple and choice reaction-time tests during the allergy season as compared with periods in which there is significantly less upper respiratory disease.³ These adverse effects of rhinitis lead to frequent absences from work or substantial decreases in productivity in the workplace. As physicians, we certainly do not want to compound these events by using drugs that exacerbate the adverse quality-of-life effects of the primary disease.

ANTIHISTAMINES

Antihistamines were first introduced in the late 1940s, and quickly became one of the best-selling drug categories of all time. These drugs are divided into two groups. The first-generation (sedating) antihistamines are those introduced before the early 1980s, and comprise the entire over-the-counter group of available antihistamines. The second-generation (nonsedating) antihista-

mines were introduced after the early 1980s, and are available only by prescription. The antihistamines in this latter group, in order of introduction, are terfenadine, astemizole, loratadine, cetirizine (mildly sedating), and fexofenadine. It is the ability of a drug to cross the blood-brain barrier that is the most important determinant of its effect on the CNS. First-generation antihistamines are small molecules that circulate in unchanged form and enter the brain readily, whereas second-generation antihistamines are large lipophobic molecules that are extensively bound to protein and have great difficulty in entering the brain.

Side effects of first-generation antihistamines

Those antihistamines that enter the brain (i.e., first-generation) have been reported to cause four different types of CNS effects: stimulatory, neuropsychiatric, peripheral, and depressive. Stimulatory effects include muscle dyskinesias, activation of epileptogenic foci, and anticholinergic stimulatory effects such as insomnia, nervousness, and tremor. Neuropsychiatric effects include hallucinations and anxiety. Peripheral anticholinergic effects include urinary hesitancy and blurred vision, whereas depressive effects are noted with both sedation and performance impairment. It is these last effects that seem to be the most problematic.

Sedation. There are several measures of sedation: sleep latency, the measure of the amount of time it takes for a study subject to fall asleep; and the critical flicker fusion test, the frequency at which a subject perceives a flashing light as a solid line. Both of these tests are objective measurements of the soporific effects of drugs. Several sleep-latency studies show statistically significant decreases in the time required to fall asleep for the first-generation antihistamines diphenhydramine or hydroxyzine, as compared with decreases in the time required to fall asleep for second-generation antihistamines, with these latter times no different than those for placebo.^{4,5} At least one of these studies found that most of those subjects having decreases in sleep latency caused by first-generation antihistamines were unaware of these sedative effects. If individuals are aware that they are drowsy, they can usually force sufficient wakefulness to complete a task. However, if they are unaware that they are drowsy, they will not be able to do this. In the workplace, this becomes a particularly important determinant of worker productivity.

Although sleepiness caused by drugs can generally be voluntarily overcome, performance impairment caused by drugs cannot be overcome until the effect of the drug wears off. A variety of studies have investigated performance impairment. Questions have been raised about

From the Department of Medicine, The University of Chicago Medical School, Chicago.

Reprint requests: Donald W. Aaronson, MD, Department of Medicine, The University of Chicago Medical School, 3500 North Lake Shore Drive, Chicago, IL 60657.

J Allergy Clin Immunol 1998;101:S379-82.

Copyright © 1998 by Mosby, Inc.

0091-6749/98 \$5.00 + 0 1/0/86489

the effects of antihistamines on learning, visual reaction times, physical reaction times, and driving. Each of these effects will be explored.

Effect on learning. One study of children with allergic rhinitis demonstrated significant learning impairment as a result of the acute symptoms of seasonal allergic rhinitis.⁶ This learning impairment was significantly exacerbated in patients treated with first-generation, sedating antihistamines, whereas treatment with second-generation, nonsedating antihistamines returned the children's school performance almost to normal. Another study compared the effects of the second-generation antihistamine loratadine with those of the first-generation antihistamine diphenhydramine in a placebo-controlled evaluation of office-work performance skills.⁷ A statistically significant negative impact of diphenhydramine was demonstrated on clerical accounting and mathematical skills, visual attention, and both visual and auditory memory, whereas there was no significant effect on these skills for either loratadine or placebo.

The impact of drugs on the P3 evoked potential is considered to be a measure of their effect on cerebral processing speed and thus on learning potential. Statistically significant slowing occurred after administration of the first-generation antihistamine chlorpheniramine, whereas there was no significant effect with either terfenadine or placebo, which differed little from each other.⁸ Thus, in situations requiring mental alertness, the presence of sedating antihistamines is clearly adverse. In addition, in dangerous occupations, such as in the construction industry, the inability to process information rapidly may result in serious injury.

Effect on visual and physical reaction times. Other measures of performance include the impact of antihistamines on: (1) dynamic visual acuity (first-generation antihistamines have been found to significantly impair visual acuity, thus impairing rapid responses to visual stimuli)⁹; (2) visual performance tests measuring reaction times (first-generation antihistamines have been found to significantly impair reaction time as compared with second-generation antihistamines, which had the same effect as placebo,¹⁰ with a resultant possibility of injury in situations requiring rapid reaction times); and (3) effects on assembly-line workers (there was a significant increase in the number of errors in subjects given first-generation antihistamines as compared with those given second-generation antihistamines or placebo).¹⁰

Effect on driving. Perhaps even more important than their effect on reaction times is the effect of antihistamines on driving performance. Greatly impaired driving behavior was noted in a group of experienced women drivers with the first-generation antihistamine triprolidine (the antihistamine in the popular over-the-counter drug Actifed) as compared with terfenadine or placebo, neither of which differed from the other.¹¹ In the study in which this was found, drivers were aware of the presence of psychologic adverse effects, but were unable to adjust their behavior to compensate for them. This would seem to make the old adage "take more care if you are taking

a first-generation antihistamine and you feel drowsy" not only incorrect, but dangerous. O'Hanlon mounted a camera on a car and measured lane weaving on the open road and in traffic after drivers took one of three study preparations: triprolidine, terfenadine, or loratadine.¹² There was a statistically significantly increased amount of lane weaving with the first-generation antihistamine triprolidine than with the second-generation antihistamines loratadine and terfenadine, which did not differ from each other. Indeed, the adverse impact of triprolidine was equal to the effect of driving with a blood alcohol level of 0.05% (the level produced by consuming approximately two cocktails). In a Canadian study of drivers killed in automobile accidents, investigators found that in accidents in which the drivers were at fault for their own fatality, they were 1.5 times more likely to have taken a sedating antihistamine as drivers killed in accidents in which the driver was found to be not at fault.¹³

Additionally, many studies have demonstrated that both alcohol and tranquilizers potentiate the adverse effects of first-generation, sedating antihistamines, but not the effects of second-generation, nonsedating antihistamines. The federal Air Surgeon has ruled that pilots and air traffic controllers may use the second-generation antihistamines loratadine or terfenadine if they have a letter from the prescribing physician noting the clinical indication for use of these drugs, the drug dosage, and a description of any adverse effects or the absence thereof.

Cardiovascular events. A variety of adverse cardiovascular events have been reported with the first-generation antihistamines doxepin, diphenhydramine, hydroxyzine, and the second-generation antihistamines terfenadine and astemizole. These reactions occur only after significant overdosing, in the presence of substantial hepatic disease or metabolic disorders, or with the concurrent administration of some macrolide antibiotics, imidazole antifungal agents, or other hepatic cytochrome P-450 inhibitors. If these drugs are not present and there is no overdosing, no adverse cardiovascular risk seems to exist.

DECONGESTANTS

In patients with nasal congestion, the first drugs used for symptomatic relief are the α -adrenergic agonists, which come in both topical and oral forms. Oral decongestants (e.g., phenylephrine, pseudoephedrine, phenylpropanolamine) have been proven effective in controlled studies. Their primary side effects are nervousness, irritability, tachycardia, palpitations, headache, and insomnia. They may also interfere with urinary flow in males, and may increase blood pressure in some hypertensive patients. Although this effect is usually minimal, these drugs should be used with caution, if at all, in patients with increased blood pressure.

Nasal decongestant sprays are readily available in the over-the-counter marketplace. Although they are potent vasoconstrictors and relieve congestion, patients using these drugs for longer than 5 to 7 days often experience

rebound congestion and/or inflammatory rhinitis medicamentosa. Topical decongestants are effective in treating the common cold, but must be discontinued within 5 days.

CROMOLYN SODIUM

Cromolyn sodium is a weak anti-inflammatory drug in the nose, but has few if any side effects. It is the drug of first choice in children under the age of 12 years, because of physicians' desire to avoid topical nasal steroids in this age group until more information is available about these drugs' side effects.

TOPICAL NASAL STEROIDS

If cromolyn is not effective, one should use topical nasal steroids intranasally. These drugs have been shown to be effective in seasonal and perennial allergic rhinitis in well-controlled, double-blind, placebo-controlled studies. In addition, they are frequently used to treat chronic sinusitis and/or nonallergic rhinitis, although the proof of their efficacy in these conditions is not as well established as it is in allergic disease. A review of the literature relative to adverse effects of topical nasal steroids reveals a very confused state of knowledge. Unanswered questions include how much systemic availability occurs with each of the products currently available, the relative potential of each of these drugs to cause adverse events, the clinical significance of hypothalamic-pituitary-adrenal axis suppression, and perhaps most importantly, whether these drugs have adverse effects on growth in children and osteoporosis in postmenopausal women.

If we look briefly at some of the reports of studies with topical nasal steroids, we find Lipworth claiming 100% absorption of fluticasone propionate from the nasal mucosa (Lipworth. Personal communication, 1996), whereas McDowell found that after 5 days of use, the maximum bioavailable quantity of fluticasone propionate was 1.8% of the dosage.¹⁴ Dockhorn et al. reported that fluticasone propionate at 200 µg/day for 1 year had the same effect (no effect) on plasma or urinary cortisol as placebo.¹⁵ Brannan et al. examined the effects of beclomethasone dipropionate and prednisone on adrenal function in a placebo-controlled study, and found that although oral prednisone significantly impaired hypothalamic-pituitary-adrenal axis responsiveness, beclomethasone dipropionate used topically was no different than placebo in having no adverse effect.¹⁶ Several uncontrolled case reports have shown significantly more recurrent acute sinusitis in patients having endoscopic sinus surgery and then being treated with fluticasone propionate than in a matched group treated with beclomethasone dipropionate.¹⁷ On the other hand, 3 patients treated with beclomethasone were found to have increased intraocular pressure that returned to normal with discontinuation of the drug.¹⁸

Perhaps more important is that a study of leg growth in pediatric patients treated intranasally with deponedrol or topical budesonide showed significant slow-

ing of growth velocity with either preparation compared with that in children treated with oral terfenadine.¹⁹ Although there are no studies of the effect of nasal steroids on osteoporosis, there are studies that show significantly decreased bone mineral density in postmenopausal women treated with inhaled corticosteroids for asthma.

Long-term follow-up of patients treated with daily beclomethasone showed no mucosal changes after periods as long as 6 years. Specifically, Mygind found no evidence of squamous-cell metaplasia, atrophic rhinitis, or increased frequency of infection in patients treated daily with beclomethasone for 1 year,²⁰ and Holopainen et al. confirmed these findings, as well as the absence of an adverse effect on plasma cortisol levels in patients treated with beclomethasone for a mean of 2.5 to 3.5 years, with some being treated for as long as 6 years.²¹

CONCLUSION

One must conclude that more evidence is needed relative to the safety of topical nasal steroids before we can provide assurance to our patients of these drugs' complete safety in the pediatric population or in postmenopausal women. However, properly informed patients should understand that the risk-benefit ratios seem to favor the use of topical nasal steroids in patients whose allergic rhinitis is resistant to oral drug therapy.

REFERENCES

1. Meltzer EO. Antihistamine- and decongestant-induced performance decrements. *J Occup Med* 1990;32:327-34.
2. Juniper E, Guyatt G. Development and testing of a new measure of health status for clinical trial in rhinoconjunctivitis. *Clin Exp Allergy* 1991;21:77-83.
3. Marshall PS. Effects of allergy season on mood and cognitive function. *Ann Allergy* 1993;71:251-8.
4. Roehrs TA, Tietz EI, Zorick FJ, Roth T. Daytime sleepiness and antihistamines. *Sleep* 1984;7:137-41.
5. Seidel WF, Cohen S, Bliwise NG, Dement WC. Cetirizine effects on objective measures of daytime sleepiness and performance. *Ann Allergy* 1987;59(6, Pt 2):48-62.
6. Vuurman EF, Van Veggel LM, Uiterwijk MM, Leutner D, O'Hanlon JF. Seasonal allergic rhinitis and antihistamine effects on children's learning. *Ann Allergy* 1993;71:121-6.
7. Adelsberg BR, D'Amico-Beadon A. The effects of loratadine, diphenhydramine, and placebo on worker productivity: results of a double blind trial. *J Allergy Clin Immunol* 1991;97:279. (Abstr).
8. Loring DW, Meador KJ. Central nervous system effects of antihistamines on evoked potentials. *Ann Allergy* 1989;63(6, Pt 2):604-8.
9. Nicholson AN, Smith PA, Spencer MB. Antihistamines and visual function: studies on dynamic acuity and pupillary response to light. *Br J Clin Pharmacol* 1982;14:683-90.
10. Walsh JK, Muelbach MD. Simulated assembly line performance following the ingestion of cetirizine or hydroxyzine. *Ann Allergy* 1992;69:195-200.
11. Betts T, Markman D, Debenham S, Mortiboy D, McKevitt T. Effects of two antihistamine drugs on actual driving performance. *Br Med J* 1984;288:281-2.
12. O'Hanlon JF. Antihistamines and driving safety. *Cutis* 1988;42(4A):10-3.
13. Warren R, Simpson H, Hilchie J, Cimbura G, Lucas D, Bennett P. Drugs detected in fatally injured drivers in the province of Ontario. In: Goldberg L, editor. Alcohol, drugs, and traffic safety. Volume 1. Stockholm: Almquist and Wikzell Publishers, 1981:p.203-17.

14. McDowall JE, Mackie AE, Bye A, Ventresca GP. Very low systemic exposure to intranasal fluticasone propionate. *J Allergy Clin Immunol* 1995;95:194. (Abstr).
15. Dockhorn R, Field E, Harding S, Rosenes P, Poliner B, Scott C, et al. Short- and long-term assessment of HPA axis effects of fluticasone propionate aqueous nasal spray. *J Allergy Clin Immunol* 1995;95:194. (Abstr).
16. Brannan MD, Herron J, Reidenberg P, Afrime MB. Lack of hypothalamic-pituitary-adrenal axis suppression with once-daily or twice-daily beclomethasone dipropionate aqueous nasal spray administered to patients with allergic rhinitis. *Clin Ther* 1995;17:637-47.
17. Mostafa BE. Fluticasone propionate is associated with severe infection after endoscopic polypectomy. *Arch Otolaryngol Head Neck Surg* 1996;122:729-31.
18. Opatowsky I, Feldman RM, Gross R, Feldman ST. Intraocular pressure elevation associated with inhalation and nasal corticosteroids. *Ophthalmology* 1995;102:177-9.
19. Wolthers OD, Pedersen S. Short term growth in children with allergic rhinitis treated with oral antihistamine, depot, and intranasal glucocorticosteroids. *Acta Paediatr* 1993;82:635-40.
20. Mygind N. Effects of beclomethasone dipropionate aerosol on nasal mucosa. *Br J Clin Pharmacol* 1997;4:287S-91S.
21. Holopainen E, Malmberg H, Binder E. Long-term follow-up of intra-nasal beclomethasone treatment: a clinical and histologic study. *Acta Otolaryngol* 1982;(Suppl)386:270-3.