

Nonsedating Antihistamines Should Be Preferred over Sedating Antihistamines in Patients Who Drive

Allergic rhinitis is very common, affecting approximately 16% of the U.S. population (1). Although therapy with intranasal corticosteroids and intranasal cromolyn has gained acceptance in recent years (2), antihistamines (H_1 -receptor antagonists) remain the first-line treatment. The possible differential effects of sedating compared with nonsedating antihistamines on driving performance and the risk for motor vehicle crashes represent an important consideration in choosing between the two categories of agents in patients who drive.

In this issue, Weiler and colleagues (3) report on a study in which they used a driving simulator to compare the effects of various agents on measures of driving performance: 60 mg of fexofenadine (a nonsedating antihistamine), 50 mg of diphenhydramine (the prototypic sedating antihistamine), alcohol (sufficient to produce an estimated 0.1% blood alcohol concentration, which is greater than or equal to the legal driving limit in all states with a specified limit), and placebo. This randomized, double-blind, single-dose study used as its primary outcome a measure known as *coherence*, the degree to which the study participant matched the speed of the vehicle that he or she was following. The investigators found that the mean coherence score after participants took diphenhydramine (0.877) was statistically significantly lower (that is, worse) than the mean score after they took alcohol (0.920), fexofenadine (0.915), or placebo (0.906). In most but not all secondary end points, scores for both diphenhydramine and alcohol were statistically worse than those for placebo but fexofenadine and placebo did not differ significantly. Weiler and colleagues also found that subjective feelings of drowsiness did not

correlate well with impairment, suggesting that patients receiving antihistamines may not be able to judge when they are impaired.

This paper adds to a large body of studies, many of which are reviewed elsewhere (4–12), showing that sedating antihistamines impair psychomotor performance or measures of driving performance under experimental conditions, such as driving simulators or road tests. These experimental studies have shown impairment after single and, less frequently, multiple doses, as well as a dose-effect relation (7). In contrast, the newer, nonsedating antihistamines have much smaller or even undetectable effects at recommended doses, although impairment sometimes occurs at higher-than-recommended doses (7). One exception is cetirizine, a newer agent whose label includes the precautions typical of sedating antihistamines.

Given that sedating antihistamines impair measures of driving performance in experimental settings, one might expect that they would also increase the risk for motor vehicle crashes in real-life settings. Two nonexperimental studies have examined the effect of antihistamine use on the frequency of motor vehicle crashes in real life. In the first of these studies, Ray and colleagues (13), using an administrative database, found a relative risk of 1.2 (95% CI, 0.6 to 2.4) for injurious motor vehicle accident associated with current use of antihistamines but detected no dose effect. Although it was not specifically stated in the paper, terfenadine, the only nonsedating agent available at the time, was excluded (Ray WA. Electronic communication, 30 September 1999). In another study using administrative data, Leveille and associates (14) found a

relative risk for injurious motor vehicle accidents of 0.7 (95% CI, 0.3 to 1.7) associated with current use of a sedating antihistamine.

What might account for the apparent discrepancy between the multiple “positive” studies in experimental settings and the two “negative” studies in nonexperimental settings? One possibility is that there is a real effect of antihistamines on the risk for motor vehicle crashes that is too small to be detected with the resolution of the nonexperimental studies. For example, by examining the 95% CIs, we can see that even though they are not statistically significant, those in Ray and colleagues’ study indicate a relative risk as high as 2.4 and those in Leveille and associates’ study indicate a relative risk as high as 1.7. Another potential reason for the discrepancy is that tolerance of the effects of antihistamines develops over time (7), which would reduce the apparent effect in nonexperimental settings, whereas most (but not all) experimental studies have been single-dose studies. A third possibility is that the relative risks in the nonexperimental studies are biased downward because being classified as “exposed” was based on having a prescription dispensed from a pharmacy rather than actually taking the drug. Thus, because participants are classified as “exposed” for a certain period after having had a prescription filled, regardless of whether they took any drug, the relative risks may be artificially reduced. Similarly, because antihistamines are available without a prescription, undetected antihistamine use among those labeled as “unexposed” may have artificially reduced the relative risks. On the other hand, other factors may have artificially inflated the relative risk. For example, a common indication for antihistamine use is allergic rhinitis, which may itself cause sedation (15). Because neither nonexperimental study attempted to account for this potential “confounding by indication” due to allergic rhinitis, the reported relative risks associated with antihistamine use may actually represent the effect of a combination of both the drug and the indication. Furthermore, both studies were performed in elderly persons, who might have a more pronounced response to antihistamines than younger persons.

Another explanation for the apparently inconsistent results is the possibility that the effects seen in experimental settings are true but do not translate into an increased risk for motor vehicle crashes in real life. For example, the “coherence” measure evaluated in Weiler and colleagues’ study (3) has not been validated as a true indicator of risk for motor vehicle crashes. Even if the measure is valid, we do not know the magnitude of change in this measure that constitutes an important level of impairment; that is, although some of the observed

differences were statistically significant, we do not know their clinical significance. Studies that correlate these experimental measures of driving impairment and the occurrence of real-life motor vehicle crashes and determine the clinically important decrement are still needed. Also important is the conduct of studies in real-life settings that overcome the limitations faced by the nonexperimental studies.

In summary, existing data indicate that usual doses of sedating antihistamines impair measures of driving performance in experimental settings, an effect not produced by nonsedating antihistamines. The clinical significance of these impairments is unknown. Studies of the risk for motor vehicle crashes in real-life settings have resulted in inconclusive to negative results. This information must be considered in light of what is known about the effectiveness of these agents: namely, that there is no established effectiveness advantage for either category. Cost should also be considered. One Internet pharmacy site recently (5 October 1999) listed the cost for loratadine and fexofenadine, the two currently available nonsedating antihistamines, at \$1.86 and \$1.69 per day, respectively. The same pharmacy listed the cost per day for the leading brand of nonprescription diphenhydramine (at doses of 25 or 50 mg four times daily) at \$0.50 to \$1.00 and the least expensive diphenhydramine product at \$0.29 to \$0.58 per day. Despite these price differences, given the lack of an established effectiveness advantage of sedating agents and uncertainties about their effect on the risk for motor vehicle crashes, the safest approach would be to preferentially initiate therapy with nonsedating antihistamines over sedating antihistamines in patients who drive. Future research on the effect of sedating antihistamines on the risk for motor vehicle crashes in nonexperimental settings may or may not ultimately alter the basis for such preferences. Unless this occurs, however, nonsedating antihistamines should generally be preferred over sedating antihistamines in patients who drive.

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