

Antihistamine effects on actual driving performance in a standard test: a summary of Dutch experience, 1989–94

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The review summarizes the major results of eight double-blind, placebo-controlled, volunteer studies undertaken by three independent institutions for showing the effects on actual driving performance of "sedating" and "nonsedating" antihistamines (respectively, triprolidine, diphenhydramine, clemastine and terfenadine, loratadine, cetirizine, acrivastine, mizolastine, and ebastine). A common, standardized test was used that measures driving impairment from vehicular "weaving" (i.e., standard deviation of lateral position (SDLP)). Logical relationships were found between impairment and dose, time after dosing, and repeated doses over 4–5 days. The newer drugs were generally less impairing, but differences existed among their effects, and none was unimpairing at doses 1–2 × the currently recommended levels. One or possibly two of the newer drugs possessed both performance-enhancing and -impairing properties, depending on dose, suggesting two mechanisms of action.

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The appearance of astemizole and terfenadine first on European (1981) and later North American (1985) markets opened the era of second-generation, or "nonsedating", antihistamines. In comparison to their predecessors, the new drugs were both more selective and less lipophilic. The older antihistamines rapidly penetrated the blood–brain barrier to block histaminergic neurotransmission, now recognized as essential for the maintenance of normal wakefulness (13). To varying degrees, they also blocked adrenergic, cholinergic, and serotonergic neurotransmission, possibly interfering with a number of other mental functions.

The prototype "nonsedating" antihistamines have since been joined on the market by similarly selective and lipophobic drugs – acrivastine, cetirizine, ebastine, and loratadine. Additions such as mizolastine are expected to appear there shortly. The respective manufacturers claim particular advantages for each drug, but all maintain that they should not cause sedation and performance impairment when taken in recommended doses.

It would be well to carefully examine this common assertion. In the strictest sense, only antihistamines that fail to cause sedation in nearly the entire patient population should be labeled as nonsedating. However, the assertion is never made in reference to

post-marketing surveillance data, which, if adequately collected, could conceivably show whether a small fraction of the total population were sedated by a particular drug. Rather, it is made on the basis of data collected by the drug's manufacturer prior to its registration. There are two sources: clinical trials with patients and psychometric studies with healthy volunteers. But one should not rely exclusively upon either source for judging that a drug is definitely nonsedating. The prevalence of patients' spontaneous reports of feeling sedated in clinical trials is almost certainly an overly optimistic estimate of the actual occurrence. It is likely that many fail to recall mild and transient drowsiness or believe such feelings are unworthy of attention when questioned days or weeks after the event. Neither should this judgment be solely based upon the lack of significant impairment in the majority of psychometric studies wherein volunteers' performance is measured in simple laboratory tests after single therapeutic doses. Sample sizes in most psychometric studies are relatively small and could not include many individuals whose sensitivity to the drugs' sedative activity lies within the top 5–10% of the normal population. The occasional sensitive individual's reaction can easily be lost among the majority's failure to react. Dose-ranging psychometric studies have rarely been un-

dertaken with the newer antihistamines. Rarer still are those involving the administration of different doses over periods long enough for the drugs' plasma concentrations to achieve steady state. Yet, such studies are the best for determining whether antihistamines are really devoid of impairing properties. If a relatively small group shows performance impairment after single or multiple doses at twice the therapeutic level, it may be assumed that at least some in the normal population will do the same after ordinary doses.

Study design is not the only questionable aspect of previous psychometric research on antihistamines: the methods employed for assessing the drugs' effects on performance also attract critical attention. It is a simple fact that no conventional test, or any collection in a battery, has ever been shown to predict medicinal drugs' effects on patients' behavior in real life. This does not necessarily mean that all conventional tests used for drug screening lack predictive validity. Many possess two of the prerequisites; sensitivity to low-level sedation and the degree of reliability that leads to highly reproducible results. Yet there is another prerequisite that none satisfies; a transfer function enabling the investigator to convert changes in test performance into some real-life analog which varies through the range of acceptable impairment into the region of unacceptable hazard. Frustration with the seeming inability of laboratory-bound investigators to satisfy the third prerequisite led others to devise an actual driving test that avoids the necessity for a transfer function. It does this by measuring a real-life performance parameter, related to patients' safety, instead of a surrogate. The method has been independently applied by three groups working at different Dutch universities in eight double-blind, placebo-controlled volunteer studies for determining whether the previously mentioned "nonsedating" antihistamines are really devoid of impairing properties, after single and multiple doses, at and above their normal therapeutic levels.

The goal of this review is to summarize and integrate the Dutch effort for showing new and old antihistamine effects on driving performance. Specific objectives are to show what impairments occur after treatments with sedating antihistamines and how these compare with that caused by the only drug that is definitely known to cause traffic accidents (e.g., ethanol); and to indicate which among the new antihistamines seem the most and least likely to cause driving impairment.

The common method

The Dutch test for assessing drug effects on driving performance evolved from studies of driver fatigue conducted in the USA during the early 1970s (7). It

was first applied in a 1981 pilot study for showing the acute effects of diazepam 10 mg (6). The test was standardized shortly thereafter (5) and calibrated in a manner allowing specification of any sedating drug's effect in terms of the blood alcohol concentration (BAC) required to achieve the same level of impairment (4). It has not changed substantially in more than 50 studies spanning more than a decade.

Subjects perform the test in the company of a safety supervisor seated in the front passenger's seat with access to redundant controls and a technician seated behind. The test involves driving over a 100-km (61-mile) circuit while maintaining a constant speed (95 km/h, 58 mile/h) and a steady lateral position within the slower traffic lane. Equipment aboard the vehicle continuously records speed and lateral position relative to lane-line delineation. The primary performance measure is standard deviation of lateral position (SDLP; cm), an index of "weaving". SDLP is a very reliable characteristic of an individual's normal driving behavior. Test-retest reliability coefficients measured for unmedicated young and middle-aged adults over periods of days, weeks, and even months are generally higher than $r = 0.75$ (5). Moreover, SDLP is very sensitive to drug-induced sedation. For example, Ramaekers et al. (9) showed the significant impairing effect of ethanol on SDLP while subjects' BAC levels declined from 0.4 to 0.2 mg/ml during the test.

Results

Nine antihistamines' effects on driving are described in the following figures. Mean changes in SDLP from the same groups' corresponding placebo levels are plotted on the ordinates. Information given along the abscissa identifies the conditions of testing with respect to each of the following: hours since drug ingestion; days after the beginning of treatment; and dose, formulation (when unusual), dosing regimen, and numbers of male and female volunteers comprising the sample. Significant ($P < 0.05$) or nearly significant ($0.05 < P < 0.10$) mean SDLP changes, indicated in the figures, were in most cases reported as such by the investigators conducting the studies. Exceptions, noted below, occurred in two cases. The results of one study (17) were judged significant if satisfying the adjusted alpha-probability criteria (P_{α_c}) for multiple mean-pair comparisons. That adjustment was ignored here for the sake of comparing this study's results with the majority which involved no adjustment. The results of another study (2) did not provide test-by-test drug and placebo comparisons but only those involving data combined over several tests in the same series. Again for comparability, these data were reanalyzed using correlated-means *t*-tests. The present authors accept

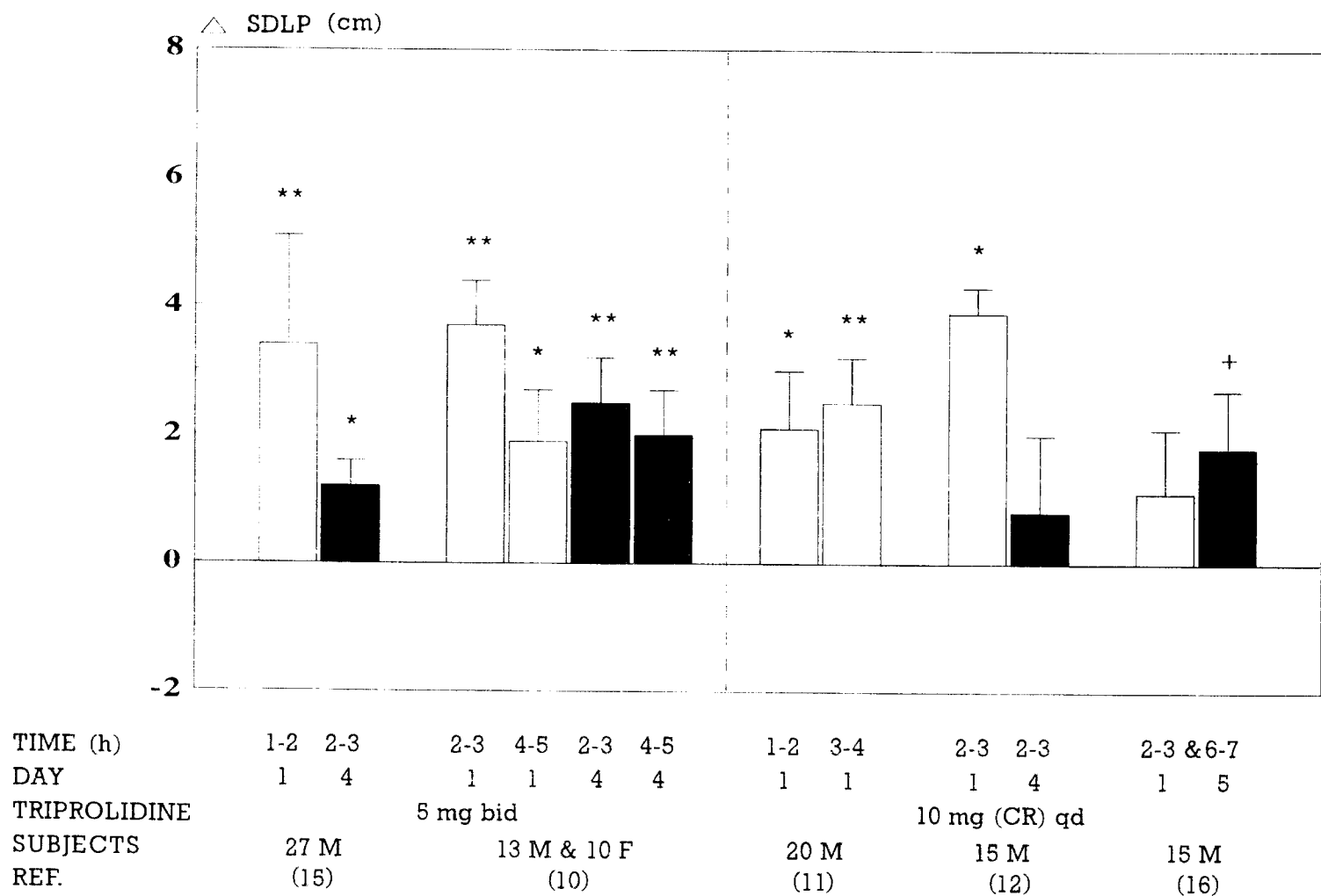


Fig. 1. Mean (+ SE) Δ SDLP (drug–placebo) after triprolidine in normal (left) and controlled-release formulations (CR; right), as measured in separate studies. Significance of changes is indicated as follows: + <0.10, * <0.05, ** <0.01.

sole responsibility for the accuracy of the results reported here for the first time.

First-generation antihistamines

Triprolidine in doses of either 5 or 10 mg (controlled-release (CR) formulation) has been used most frequently as an active control (Fig. 1). The acute effects of triprolidine 5 mg on SDLP were remarkably similar in the two studies where it was employed. A reduction in those effects was observed after 4 days of twice daily dosing in both cases, indicating tolerance for triprolidine’s sedative activity. However, tolerance did not abolish the acute effect entirely: a significant effect was still present for 4–5 h after the last dose. The effects of the controlled-release formulation were appreciably less but still significant for up to 3–4 h after the first dose. Substantial tolerance was seen after four consecutive daily doses in one study, but not after five daily doses in another.

Single doses of diphenhydramine 50 mg and clemastine 2 mg were respectively given to women and a mixed-gender group in separate studies (Fig. 2). Both drugs produced large elevations in SDLP. Interestingly, the women in the latter study reacted significantly ($P<0.05$) more than their male counterparts to clemastine 2 mg; mean Δ SDLP for the former was 5.7 cm, and for the latter, only 2.5 cm.

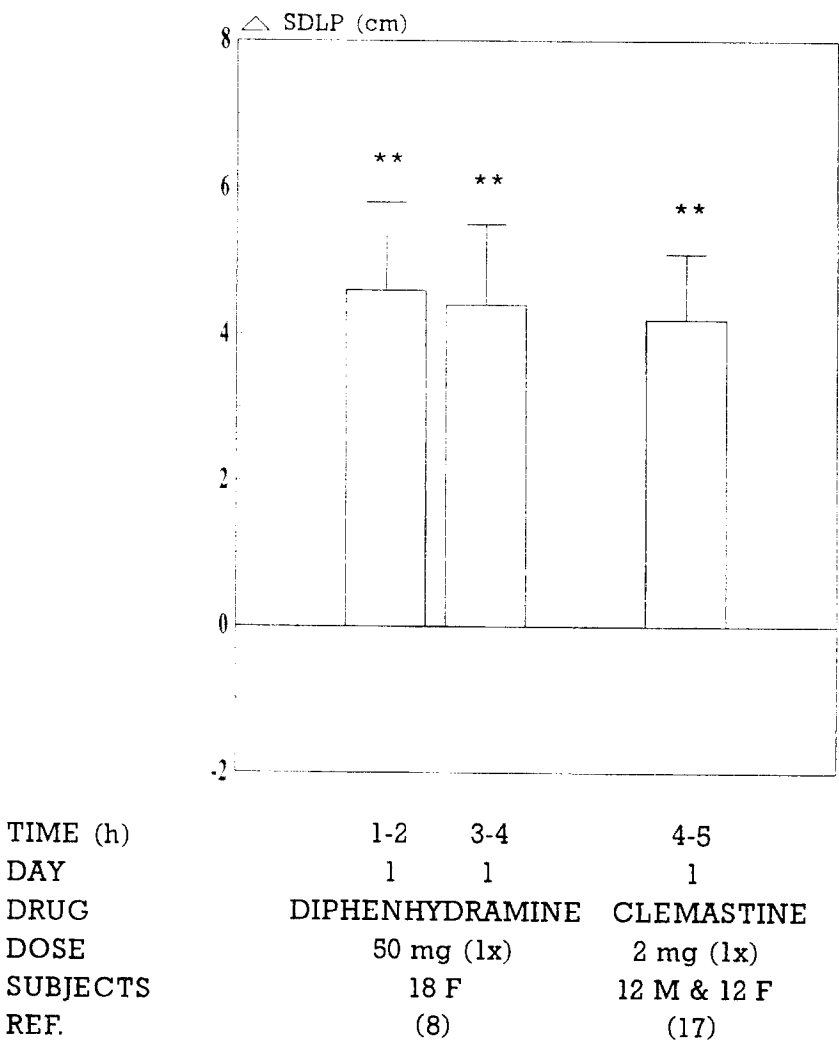


Fig. 2. Mean (+ SE) Δ SDLP after single doses of diphenhydramine and clemastine in separate studies. Significance of changes is as indicated in Fig. 1.

These results seem representative of the adverse effects of first-generation antihistamines on SDLP. Their clinical relevance can be judged in comparison to those of various BACs measured in the alcohol-calibration study (4), mentioned above. Twenty-four male and female “social drinkers” drove while sober and then after consuming enough alcohol to raise their BACs to 0.3, 0.6, 0.9, and 1.2 mg/ml on separate occasions. Their mean Δ SDLP values increased systematically as an exponential function of BAC (mean correlation, $r = 0.99$). This relationship was described by an equation which indicates that BACs of 0.5 and 1.0 mg/ml respectively produce Δ SDLP values of 2.2 and 5.5 cm. All changes produced acutely by first-generation antihistamines fell within this range. The inference is that clinically important driving-performance impairment can occur after first-generation antihistamines.

Terfenadine

Terfenadine has been given in five separate studies in single doses up to 180 mg, and multiple doses over 4 days, up to 120 mg b.i.d. (Fig. 3). No single dose ever produced a significant rise in SDLP. On the contrary, there was a tendency for 60 and 120 mg to produce a slight fall in SDLP, suggesting a mild stimulating activity of the drug. Multiple doses of

60 mg b.i.d. or 120 mg q.d. were likewise without a significant effect. However, after subjects had been treated with twice the therapeutic dose, 120 mg b.i.d., for 3 days and tested after the morning dose on the fourth, terfenadine finally became significantly impairing.

Loratadine

Loratadine produced no significant rise in SDLP after single doses of 10 and 20 mg, or after multiple 10 mg q.d. doses in four studies (Fig. 4). Yet, it, too, had a significant impairing effect when given over 4 days in twice the therapeutic dose, 20 mg q.d. Mean Δ SDLP measured in morning and afternoon tests on the first and last treatment days failed to differ significantly from corresponding placebo levels. However, the associated P values closely approached significance ($P = 0.06, 0.09, 0.09$, and 0.06 , respectively), and the overall drug effect was significant ($P < 0.05$).

Cetirizine

Cetirizine’s effect on SDLP is a matter of contention between different groups of investigators (Fig. 5). One showed a significant impairing single-dose effect of cetirizine 10 mg, while the other found no

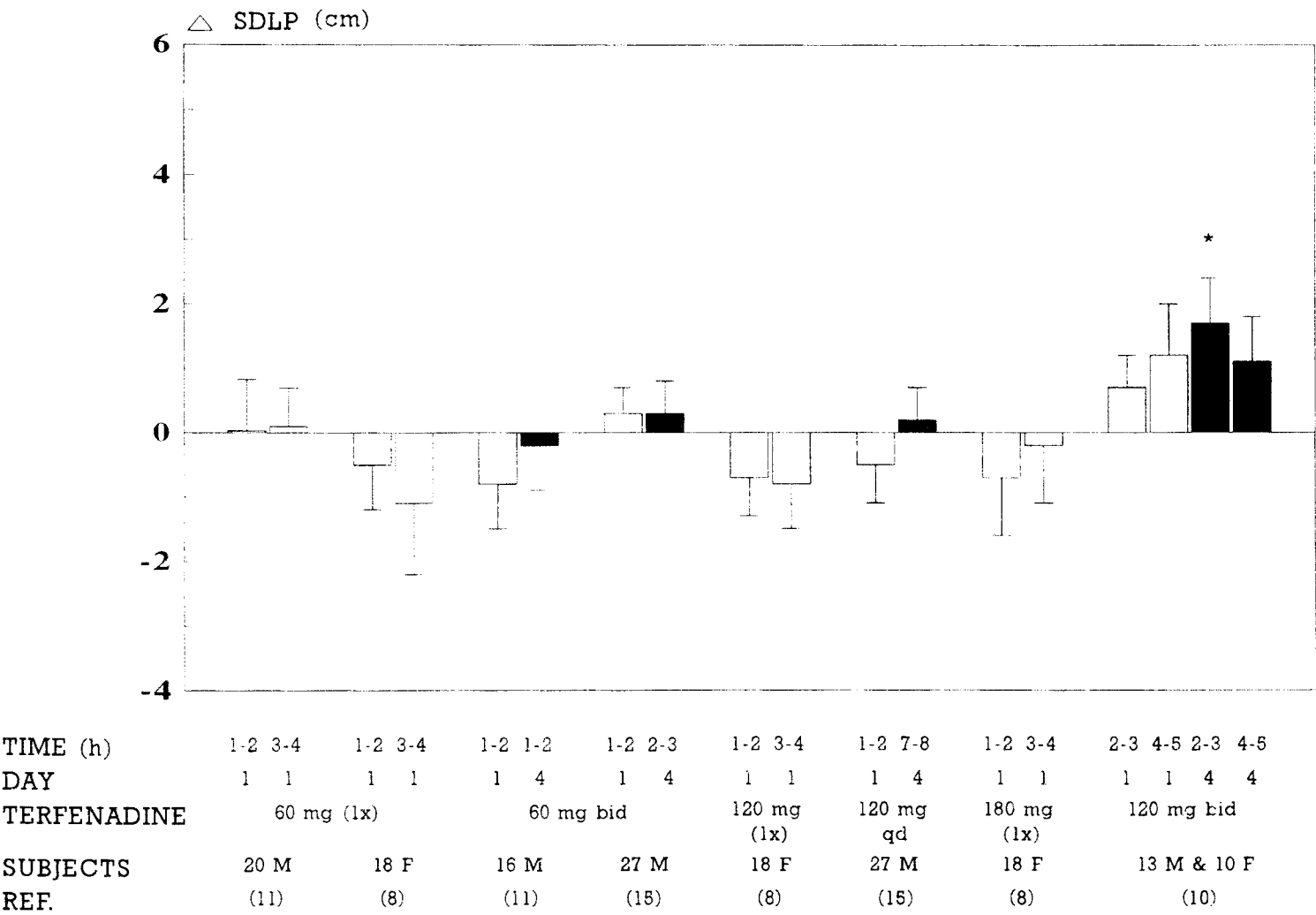


Fig. 3. Mean (+ SE) Δ SDLP after terfenadine. Significance of changes is as indicated in Fig. 1.

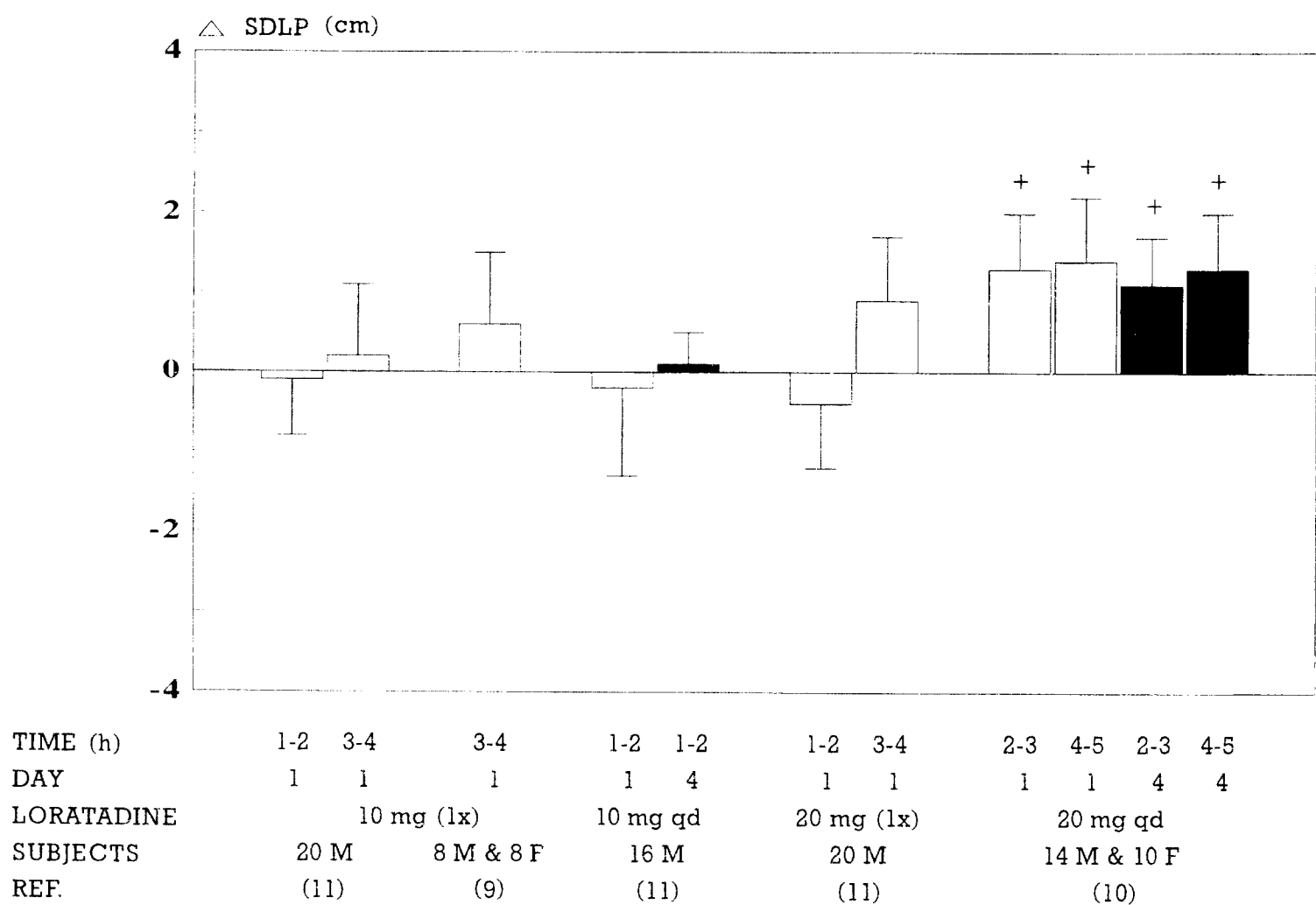


Fig. 4. Mean (+ SE) Δ SDLP after loratadine. Significance of changes is as indicated in Fig. 1.

effect of that dose on either the first or fourth days of repeated administration. However, differences in the composition of the respective subject samples and the times when they were tested may explain this disparity. The study showing an effect employed a mixed-gender sample who were tested 3–4 h after drug administration. That showing no effect employed a male sample who were tested 1–2 h after the first dose and 7–8 h after the last. Though the former investigators were unable to measure a significant gender effect, possibly owing to the small numbers of each sex, the results mentioned above and below suggest that women are more sensitive to antihistamines' sedating activity. Moreover, their subjects were tested closer to the time when cetirizine's pharmacodynamic effects in the wheal and flare test are maximum (14). It is therefore possible that the latter investigators failed to measure a significant drug effect due to the relative insensitivity of male subjects and an inappropriate time of testing, particularly on treatment day 4.

Acrivastine

In Europe, acrivastine is available alone in 8-mg doses and combined with the decongestant, pseudoephedrine, in two formulations: acrivastine 8 mg/pseudoephedrine 60 mg (instant release) and acriv-

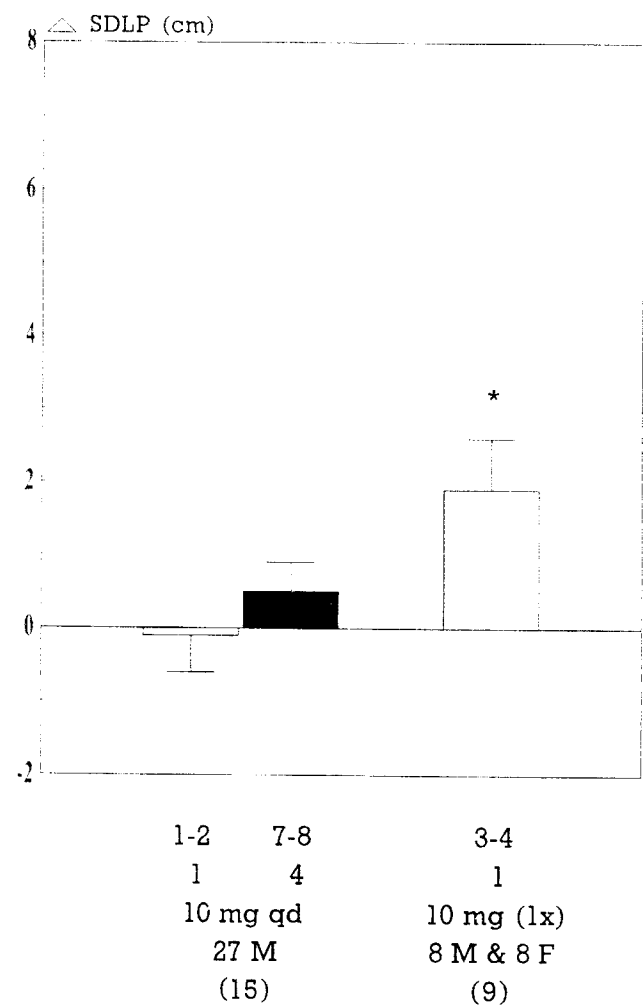


Fig. 5. Mean (+ SE) Δ SDLP after cetirizine. Significance of changes is as indicated in Fig. 1.

astine 12 mg/pseudoephedrine 90 mg (slow release). Only the combination, acrivastine 8 mg/pseudoephedrine 60 mg (instant release), is available in the USA.

Two studies were conducted to measure the effects of acrivastine alone in doses of 8, 16, and 24 mg and both combination preparations (Fig. 6). Acrivastine 8 mg had no effect on mean Δ SDLP in male subjects but a significantly impairing one in females. Moreover, the women tended to drive worse as the doses ascended. The duration of their impairment was also dose-related.

The addition of pseudoephedrine in the combination preparation had a salutary effect on driving performance. The women who were impaired after 8 mg of acrivastine alone were not affected by the same dose in combination with pseudoephedrine 60 mg. Moreover, the men who were treated with that combination drove, after 4 days of treatment, with a significantly lower SDLP than after placebo. It would appear that pseudoephedrine's mild stimulating activity physiologically antagonizes acrivastine's correspondingly mild sedating activity, when present; and that the former predominates when the latter is low or absent.

Mizolastine

Mizolastine is a relatively new astemizole derivative. It will be marketed in 10-mg doses to be taken once daily. Mizolastine's effects on SDLP after single doses of 5, 10, 20, and 40 mg were measured in a single study (Fig. 7). As expected, 20- and 40-mg doses had significantly impairing effects. How one judges the significance of the 10-mg dose effect depends upon his interpretation of the criterion. Originally, an alpha-probability adjustment was used for multiple drug-placebo comparisons, and the effects of 10 mg failed to meet the significance criterion ($P = 0.036$; $P\alpha_c = 0.025$). However, it would appear from the well-defined dose-effect relationship that impairment begins after a single dose of about 10 mg. Whether or not one wishes to accept the original or present interpretation would depend upon his preference for avoiding a type I or type II error.

Ebastine

Ebastine's chemical structure and metabolism closely resemble those of terfenadine. Both piperidine derivatives are prodrugs almost entirely transformed

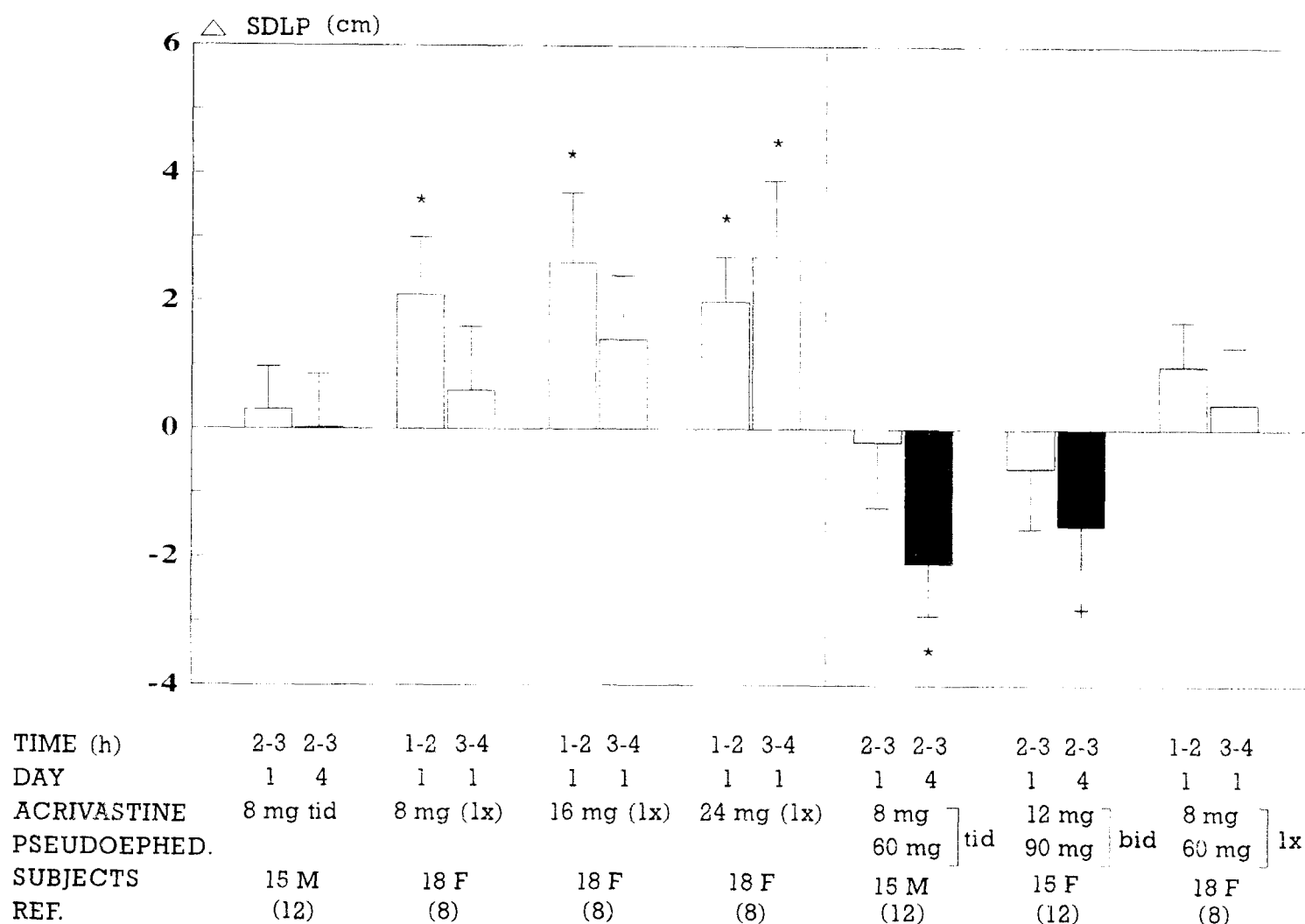


Fig. 6. Mean (+ SE) Δ SDLP after acrivastine alone (left) and in combination with pseudoephedrine (right). Significance of changes is as indicated in Fig. 1.

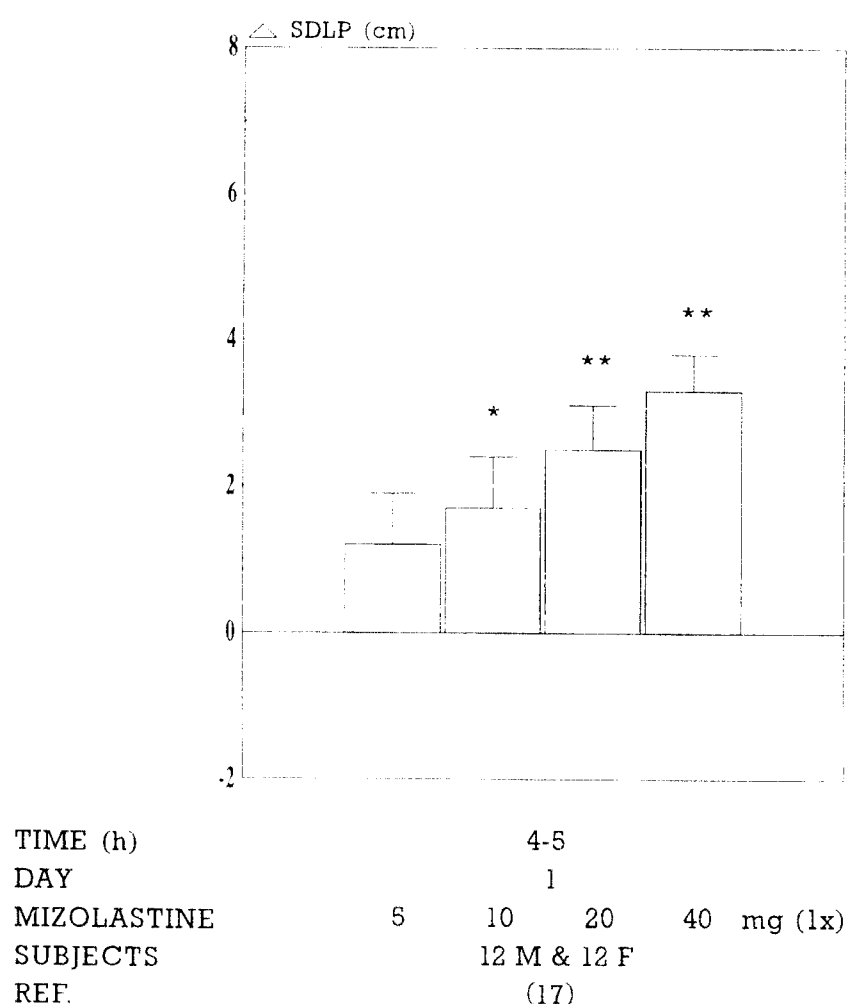


Fig. 7. Mean (+ SE) Δ SDLP after single doses of mizolastine. Significance of changes is as indicated in Fig. 1.

into active acid metabolites during first-pass metabolism. Ebastine was registered for 10 mg q.d. dosing in its country of origin (Spain), but doubts concerning that dose's efficacy may cause its registration for 20 mg q.d. dosing elsewhere.

Fascinating results emerged from the single study involving ebastine (Fig. 8). Male subjects were treated with ebastine 10, 20, and 30 mg q.d. for 5 days on separate occasions. They undertook the driving test twice on both the first and last days of each series. The results were published twice, first in a technical report (6) with limited distribution and later in the general literature (2). The former report was the more comprehensive and is taken as the source of data for the following.

Ebastine 10 mg significantly lowered mean SDLP relative to placebo. Higher doses were said to have no significant effects but primarily because the investigators combined data from all tests for making the drug-placebo comparisons. Reanalysis of the data from day 5 of ebastine 30 mg treatment showed that this dose was significantly impairing.

The results shown in Fig. 8 provide much food for thought. There was apparently a shift in ebastine's CNS activity from stimulating to sedating as its brain concentration rose with the dose and/or accumulation. The effects of the 10-mg dose were apparently stimulating on both test days. The 20-mg dose low-

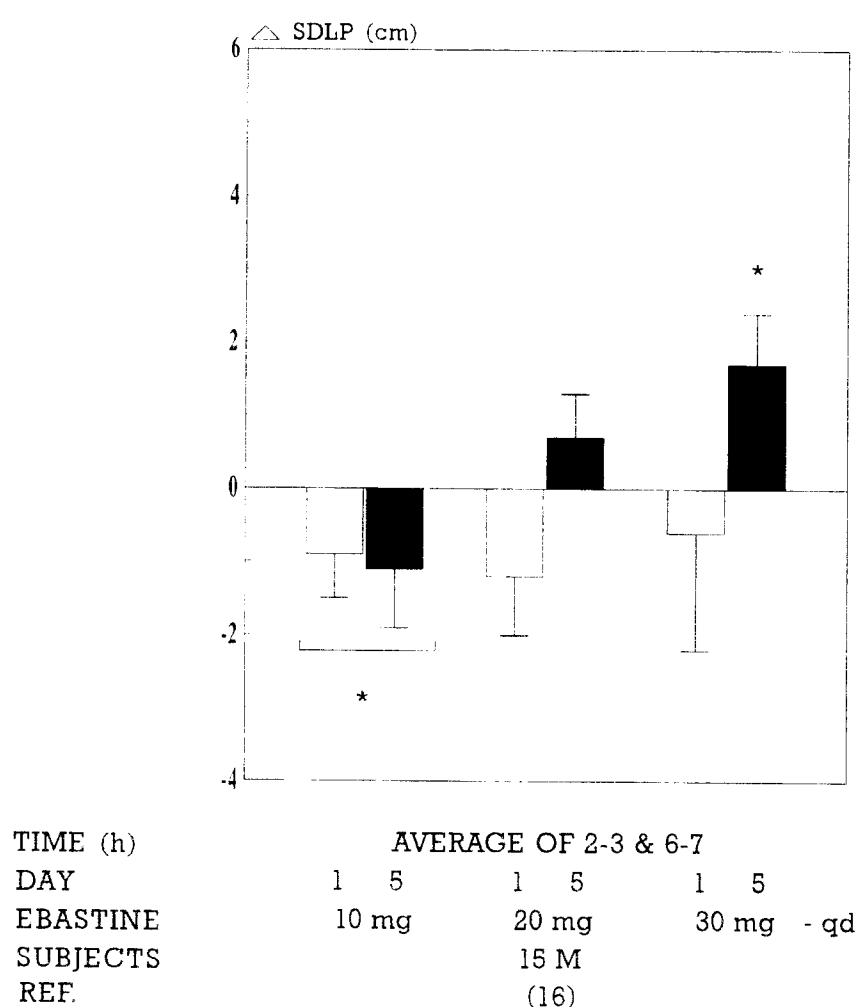


Fig. 8. Mean (+ SE) Δ SDLP over two tests given on same days after ebastine. Significance of changes is as indicated in Fig. 1.

ered SDLP on day 1, though not significantly, suggesting that it too might be stimulating. All suggestion of a stimulating effect was gone when this dose's effects were measured again on day 5. The 30-mg dose had little effect on mean Δ SDLP but a relatively large effect on the variance of individual values on day 1. By day 5, the highest dose's effects were clearly in the direction of sedation, and a contraction of the variance showed that this was relatively consistent for all subjects.

Discussion

The results of the Dutch effort are in general accord with the commonly observed difference in the impairing effects of first-generation and second-generation antihistamines. Even when those studies showed a significant driving impairment after therapeutic doses of the newer antihistamines, its magnitude was always much less than the effects of the older drugs. Except after doses that were 2–3 $\times$ higher than currently recommended, no second-generation antihistamines ever produced as much impairment as ethanol in a blood concentration of 0.5 mg/ml. Obviously, newer antihistamines are all much safer than their predecessors for use by patients who drive.

Yet, an important message from the Dutch studies is that every second-generation antihistamine

possesses properties that can impair driving performance: none is truly nonsedating irrespective of the dose and duration of dosing. Therapeutic doses of some, like terfenadine and loratadine, are apparently unable to produce a significant effect in a sample of 20–30 healthy volunteers. However, these drugs significantly impaired volunteers' driving performance after repeated doses that were only twice as high. It seems likely that normal doses would do the same in a small fraction of the total user population. All patients should be warned accordingly.

Other drugs – acrivastine, mizolastine, and possibly cetirizine – appear to possess slightly greater sedating properties. For acrivastine, this property can be overcome by the mild sympathomimetic effects of the decongestant with which it is presented in a combination preparation. A laboratory-based psychometric study (3) has shown that the combination of azatadine, a sedating antihistamine, with pseudoephedrine resulted in a net effect on performance that was indistinguishable from placebo's. The components in this case had the expected significant impairing and improving effects. Acrivastine 8 mg combined with pseudoephedrine 60 mg also improved the driving performance of male subjects after 4 days of repeated dosing. The combination had no significant effect in women tested after a single dose, but might have similarly improved their driving performance after a multiple dose series.

Uncertainty regarding the impairing properties of cetirizine 10 mg was not resolved by two driving studies providing conflicting results. An answer could emerge from a third study using the same approach for testing cetirizine's effects across a wide dose range, but it might be available now from another source. Betts et al. (1) measured 10 female volunteers' driving performance in a series of closed-course vehicle-handing maneuvers such as driving through a slalom demarked by pylons and through a gap between pylons judged to be just wider than the vehicle. After a single dose of cetirizine 10 mg, these subjects' performance was little different than after placebo. After 20 mg, however, they struck significantly more pylons in both tests. Without bothering with the arid question of whose driving tests are the most sensitive, it is clear that both approaches provide about the same results when applied to measuring the effects of a drug regarded clinically as sedating. It would be surprising, therefore, if application of the Dutch method failed to show a significantly impairing effect of cetirizine 20 mg. In that case, the present controversy about the effects of 10 mg would become largely irrelevant for the reason given above.

Ebastine's effects on driving performance are at once puzzling and provocative. No antihistamine should be intrinsically stimulating at one dose and

sedating at another if it is solely an H_1 -receptor antagonist. The possibility exists that ebastine's metabolite, carebastine, is something more.

Postsynaptic H_1 and H_2 receptors have been located in the brain and also a presynaptic autoreceptor, H_3 (13). An intense effort is now underway to develop ligands that bind as agonists or antagonists at the H_3 receptor. According to current theory, H_3 agonists should be sedating, and antagonists, stimulating. Carebastine is known to be an H_1 ligand, but it may also bind preferentially at the autoreceptor. This would nicely explain the driving test results; initial stimulation followed by eventual sedation as the drug's rising brain carebastine concentration antagonizes first H_3 autoreceptors and then postsynaptic H_1 receptors. Whether carebastine acts in this manner should be determined by future research.

The suggestion from the results of several studies that women might be more susceptible to antihistamine-induced sedation should also be addressed in future research. Perhaps women's generally smaller volume of distribution that results in somewhat higher plasma drug concentrations after any dose is the responsible factor. But if any factor is operating to produce a gender difference in sensitivity, the usual choice of exclusively male samples for studying antihistamine and other drugs' effects on performance is an obvious mistake. The mere suspicion that this difference exists should henceforth alert researchers to employ either mixed-gender subject samples or those comprised exclusively of the gender which presently seems the more sensitive.

Conclusions

- All of the previously mentioned second-generation antihistamines are clearly less sedating and impairing than their predecessors.
- But none of them is entirely devoid of CNS activity.
- All produce driving-performance impairment indicating a low level of sedating activity after single or multiple doses 1–2 × those currently recommended.
- At least one has stimulating activity which gives way to sedating activity as its brain concentration rises with the administered dose and/or accumulation, and its effect on driving performance varies accordingly.
- Combined therapeutic doses of sympathomimetic decongestants and mildly sedating second-generation antihistamines have a net effect on driving performance that is determined by the components' physiologically antagonistic CNS activities. The average net effect for combination preparations so far studied was slightly performance enhancing or nil. Other combinations might

have the same or different effects, and individual reactions to all are likely to be less consistent than to either component separately.

- Finally, warnings about antihistamines' possible adverse effects on driving and other potentially dangerous activities should not be waived for the second-generation drugs. It is unlikely that the majority of patients taking recommended doses of any of these drugs will experience untoward reactions affecting their driving safety, but if any fraction will, all patients should receive an appropriate warning.

Acknowledgments

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