Effects of Terfenadine on Psychomotor Performance
An Overview

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Summary

Sedation and impairment of psychomotor performance are well known adverse effects of the traditional antihistamines. These effects appear to be caused by different mechanisms, but both may have potentially dangerous consequences. While several of the newer antihistamines, such as terfenadine, have overcome the problem of sedation, it is also important to establish their propensity to cause psychomotor impairment.

Many single- and multiple-dose studies (mostly in healthy volunteers) have compared the effects of terfenadine on psychomotor performance with those of placebo, as well as traditional and other nonsedating antihistamines. Over half of the studies employed divided-attention tasks that are considered relevant to everyday activities, such as driving. Like several other nonsedating antihistamines, single doses of terfenadine of up to 120mg did not impair driving performance and generally had no significant effects on other psychomotor tests compared with placebo. In most of the multiple-dose studies, terfenadine 60mg twice daily was administered for up to 5 days. Again, the effects of terfenadine on psychomotor performance differed little from those of placebo.

Thus, the available evidence suggests that the problem of impaired psychomotor performance associated with the older, traditional antihistamines does not apply to terfenadine.

Drowsiness (sedation) and the impairment of psychomotor performance [i.e. impairment of the performance and coordination of certain muscular movements in response to stimulation of the central nervous system (CNS)] are well recognised effects associated with the use of traditional antihistamines (e.g. diphenhydramine). Drowsiness has been attributed to several mechanisms, including blockade of central histaminergic receptors and inhibition of histamine-N-methyl transferase (Luscombe et al. 1983; Nicholson & Stone 1982, 1983). However, the mechanism(s) involved in impairment of psychomotor performance remain unclear.

It is important to recognise that drowsiness and
impairment of psychomotor performance, although both CNS effects, can be distinguished (Betts et al. 1989; Clarke & Nicholson 1978; Goetz et al. 1989; Unchern et al. 1986). Drug effects on psychomotor function are assessed by objective testing, whereas sedative effects are usually indicated by subjective evaluation (e.g. patients complete questionnaires and any adverse effects are assigned visual analogue scale scores). Although a number of non-sedating antihistamines are now widely available, it is conceivable that these drugs may affect psychomotor performance.

The CNS effects of traditional antihistamines have been associated with considerable social and economic consequences, such as inability to perform functions requiring alertness or motor coordination. Although the contribution of antihistamine use to automobile accidents has been questioned by some investigators (Jick et al. 1981; Skegg et al. 1979; Williams et al. 1985), others have reported an association between use of certain antihistamines and fatal motor vehicle accidents (Cimbur et al. 1982; Finkle et al. 1968; Garriat et al. 1977; Starmer 1985). This emphasises the need to distinguish between types of CNS effects and the need to examine individual antihistamines for their effects on psychomotor performance.

Terfenadine was the first non-sedating antihistamine to be marketed in the US. Its CNS effects, including those on alertness and psychomotor performance, are not significantly different from those of placebo (McTavish et al. 1990; Weiner 1982). This is well supported by the pooled results of clinical trials, many of which were double-blinded and placebo-controlled, in several thousand patients with various disorders (Masheter 1989; Rombaut & Hindmarch 1991; Woodward 1988). Animal studies indicate that terfenadine, unlike many of the traditional antihistamines, does not readily penetrate the blood-brain barrier (Leeson et al. 1982, 1985), and this is probably related to the low level of CNS effects associated with the drug.

1. Clinical Trials

The majority of data included in this review of the effects of terfenadine on psychomotor performance are derived from the published literature up to December 1991, but unpublished data have also been incorporated. A total of 33 studies have been identified (19 single-dose and 14 multiple-dose) that used objective parameters to assess the effects of terfenadine on psychomotor performance relative to those of placebo and other antihistamines. All except one of the studies involved healthy volunteers. In 1 multiple-dose trial, the psychomotor effects of terfenadine were studied in hay fever sufferers (Beaumont et al. 1990).

A wide variety of tests has been employed to assess these effects (Hindmarch 1980). Although some of the tests are complicated and difficult to replicate (Hindmarch 1980), it is important to realise that drug effects can rarely be fully predicted from a single performance test (Broadbent 1984), and in some cases, a given test when used alone, such as a steering test or the weaving index, may be less sensitive to CNS effects. For optimum evaluation, tests should simulate the practical situation (e.g. actual or simulated driving tests) or a battery of performance tests should be employed to obtain a more complete effect profile (Broadbent 1984). Divided-attention tasks are the most sensitive tests for assessing psychomotor function, providing results from, or results which may be extrapolated to, ‘real-life’ situations. Of the 33 studies cited, 17 (52%) included at least 1 divided-attention task in their design: actual driving (n = 7); simulated driving (1); tracking plus memory tasks (1); choice reaction time (8), and visual search and tracking tasks combined (3).

In single-dose trials, drug effects are dependent on the interval following administration. Thus, postdose testing times have been included in table I. In most of the multiple-dose trials summarised in table II, psychomotor testing was performed when plasma drug concentrations were at steady-state.

1.1 Single-Dose Studies

Most of the single-dose data indicate that terfenadine does not impair psychomotor performance (table I).

The effects of terfenadine were not significantly different from those of placebo in 15 of 19 studies