RESIDUAL ("HANGOVER") EFFECTS OF FLURAZEPAM HCL UPON THE ACTUAL DRIVING PERFORMANCE OF OCCASIONAL HYPNOTIC USERS:

II. SUBCHRONIC EXPERIMENT

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SYNOPSIS

Four women who previously served as subjects in a larger study of flurazepam HCL's "acute" residual effects volunteered as subjects for a "subchronic" investigation of the drug. They were treated for 2 nights with a placebo, 8 nights with flurazepam 30 mg, and 3 nights with placebo, in that order. They performed a standard driving test in both the morning and afternoon following (1) the 2nd placebo treatment (i.e. baseline-placebo), (2) the 2nd, 4th, and 7th drug treatments, and (3) the 3rd and 5th placebo treatments (washout-placebo). The tests consisted of operating a specially instrumented vehicle over a 100-km highway circuit while attempting to maintain a constant speed (95 km/hr) and lateral position in the right (slower) traffic lane. These parameters were continuously measured. Relative to baseline-placebo performance levels, the subjects showed an impaired ability to control lateral position after 2 drug treatments, greater impairment after 4 treatments, and only partial recovery after 7 treatments. Their recovery was complete on both test days in the washout-placebo period. Tolerance for the residual effects of flurazepam 30 mg seemed to develop slowly during repeated nightly treatment and was incomplete after a week.

INTRODUCTION

In the companion article (see O'Hanlon et al., this volume) to this one we described an "acute" residual effect of flurazepam HCL (Dalmane, Dalmadrom) upon aspects of the actual driving performance of occasional hypnotic drug users. In particular, the results of the acute experiment revealed a relatively large and persistent effect of flurazepam 30 mg upon 24 subjects' lateral road-tracking error. This effect could be serious with respect to the driving safety of habitual flurazepam users if it is not countered by the occurrence of pharmacological tolerance,

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that is, by a progressive reduction of the residual sedative effect over days of continual drug use.

The literature arising from the application of laboratory test batteries to subjects treated nightly with flurazepam 30 mg is ambiguous and contradictory. Some investigators found no daytime residual effects after 1 or 2 weeks of flurazepam treatment (Linnoila et al., 1980), whereas others saw impaired performance in some tests but not others following 4-7 consecutive treatment nights (Church & Johnson, 1979; Salkind & Silverstone, 1975; Vogel et al., 1976). The reason for this disparity is unknown as is the practical relevance of all results obtained using conventional laboratory test procedures.

The present "subchronic" study was an extension of that reported in the companion article. The purpose of the subchronic study was to determine whether the performance of a sub-sample of the original group would recover while the subjects continue to use flurazepam 30 mg over 8 consecutive nights. If recovery is the case, it will considerably reduce the importance of driving performance changes observed after the subjects had been treated with flurazepam 30 mg on each of 2 consecutive nights in the acute experiment. If, on the other hand, recovery is incomplete or entirely absent, the results increase the importance of the earlier findings.

The present study should not be thought of as a stand-alone investigation of flurazepam 30 mg's subchronic effects. Nonetheless, it clearly reveals the value of following the demonstration of an acute drug effect with an indication of how the acute effect changes as a consequence of continuing therapy.

**METHOD**

**Subjects**

Four subjects (female) who had participated in the previous experiment volunteered to continue in the subchronic experiment. Their characteristics are listed in Table 1.

"Normal proficiency" was measured by determining the respective subjects' standings in relation to all subjects on the basis of SD lateral position measurements from both tests combined in Condition Placebo (P) of the acute experiment. These are given as Z-scores determined as the difference between individual measurements and the group mean, relative to the group standard deviation. The scores indicate that the subjects were fairly representative of the group in this respect.
"Flurazepam sensitivity" was determined in a similar manner by deriving Z-scores from the changes in SD lateral position from Conditions P to F 30 (flurazepam 30 mg). Two subjects were especially sensitive, and 2 normally so.

Procedure

The participation of each subject lasted for 13 consecutive days. This interval was divided into 3 periods: placebo-baseline, 2 days; drug treatment, 8 days; and placebo-washout, 3 days. A placebo was administered at 2200 hours on the nights before each of the placebo-baseline and placebo-washout days and a 30-mg dose of flurazepam HCL was administered (p.o.) at the same time on the nights preceding each of the drug-treatment days. The placebo and the drug were administered single-blind (240 mg, total). Morning and afternoon tests were given on the following days: 2nd in the placebo-baseline period; 2nd, 4th, and 7th in the drug-treatment period; and 1st and 3rd in the placebo-washout period. The control and testing procedures were the same as in the previous experiment with one exception: Owing to the later sunrise during the months of the subchronic experiment (that is, December-January), the beginning of the morning test was advanced from 0800 hours to 0900 hours. Thus, this test transpired between 0900 and 1000 hours, or 11-12 hours post-administration. The time of the afternoon test was, however, unchanged: that is, at 1400 - 1500 hours or 16-17 hours post-administration.

RESULTS

Only SD lateral position was analyzed in detail. The other objective performance data were inspected and seen to conform with data obtained in the previous experiment.

The SD lateral position varied over days both for individuals and the group (Figure 1). Every subject showed the following:

1. A relatively low (that is, good) level of SD lateral position in both tests on the placebo-baseline day.

2. An increase in SD lateral position following the 2nd night of drug treatment.

For the group as a whole, there was a further rise in SD lateral position from the 2nd to the 4th drug-treatment day, but a fall, particularly during the afternoon test, from the 4th to the 7th drug-treatment day. Performance recovered nearly to the baseline level on the 1st washout placebo day, and entirely on the 3rd washout-placebo day.
The significance of individual changes in SD lateral position over days could be determined using MANOVA by treating the 10 successive 10-km measurements within each test as the source of the error term. Naturally, the results of an analysis of each subject's data can only be generalized to the individual concerned. Yet, if all, or nearly all, of the results from separate individual analyses are similar, some guarded inferences are possible on a larger scale. Relative to their respective baseline-placebo levels (morning and afternoon, combined), 3 subjects showed significantly elevated SD lateral position on the 2nd drug-treatment day; all 4, on the 4th drug-treatment day; and 3, again, on the 7th drug-treatment day. The performances of all 4 subjects on both the 1st and 3rd washout-placebo days were not significantly different from their respective baseline-placebo levels.

**DISCUSSION**

The results indicate that the development of pharmacological tolerance for flurazepam 30 mg's residual effects is a slow process. The worst effects of flurazepam occurred after 4 successive nights of treatment. There was a suggestion of recovery due to the development of tolerance following a week of treatment, but this was mainly provided by results obtained in the afternoon test.

The statistical tests were confined to separate analyses of each subject's data. This approach was required by the small sample size; it could have lead to erroneous conclusions were there any factors causing significant changes in SD lateral position from day to day, besides flurazepam. However, the fact that there were no significant changes from the placebo-baseline day to either of the placebo-washout days, indicates that flurazepam was the only effective factor.

The lack of any significant changes from placebo-baseline to at least the first placebo-washout day was somewhat surprising in view of the well-known persistence of flurazepam's active N-desalkyl metabolite in the body (Greenblatt et al., 1975). A period of 34 hours elapsed between the final drug treatment and the beginning of the first morning placebo-washout test. At the latter time the plasma N-desalkyl concentration was still relatively high, even higher than it was throughout the day following 2 successive treatments. Yet performance on the first placebo-washout day was practically the same as it had been on the baseline-placebo day and superior to that observed immediately following 2 nights of treatment. The conclusion must be that N-desalkyl flurazepam is not the only factor.
responsible for performance impairment and may not even be the most important. Since the parent compound is not present in appreciable plasma concentrations during days following night-time flurazepam ingestion, the only apparent candidate remaining as the agent responsible for the residual effect is flurazepam's 2-hydroxyethyl metabolite. The plasma pharmacokinetic profile of 2-hydroxyethyl-F is poorly defined. Yet the substance is measurable in plasma for about 24 hours following flurazepam ingestion (Kaplan et al., 1973). It could be a responsible factor in addition to, or instead of, N-desalkyl-F.

Note

Uncertainty regarding the cause of the residual flurazepam effect may be dispelled when blood samples taken after all tests in both the acute and subchronic studies are completely analyzed. Initially these were assayed for N-desalkyl-F, only. But when we appreciated that neither mean nor individual performance changes could be explained by correlations with plasma N-desalkyl-F concentrations, new assays were ordered, this time for 2-hydroxyethyl-F. The results were not available in time for this publication. These will be reported in a subsequent communication.

ACKNOWLEDGMENTS

This research was sponsored by F. Hoffmann-La Roche & Co. Ltd. (Basle, Switzerland), the manufacturer of flurazepam HCL. If it contributes to the safer use of hypnotics by drivers, it should not be forgotten who was responsible. The authors wish to commend that corporation for its ethics and feelings of responsibility for the safety of its products' users.

Medical supervision was provided by Prof.dr. H. Wesseling, Institute of Clinical Pharmacology, University of Groningen. Daily medical assistance was accomplished by drs. T. de Vries. The authors are deeply grateful for their assistance.

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