Flurazepam Effects on Sleep EEG

Visual, Computer, and Cycle Analysis

Irwin Feinberg, MD; George Fein, PhD; James M. Walker, PhD; Leonard J. Price, PhD; Thomas C. Floyd, MA; Jonathan D. March

Analysis of sleep effects of flurazepam hydrochloride on four normal subjects confirmed that this drug substantially suppresses both REM and stage 4 sleep. Computer analysis disclosed that delta wave amplitude was greatly reduced by flurazepam. However, low density delta wave activity (ie, stage 2 sleep, which was increased in duration beyond the reduction in stage 4), permitted the number of delta waves and the time they occupied per night to remain at baseline levels. This finding suggests that sedative-hypnotics increase total sleep time by slowing the metabolic processes of sleep so that a longer sleep duration is required for the same biological effects. New observations on the induction times of REM and stage 4 effects are also presented. In general, the distortions in sleep EEG produced by flurazepam qualitatively resemble, but are quantitatively greater than, those produced by barbiturates in equivalent hypnotic doses.

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The sleep EEG has been of special interest to those concerned with hypnotic effects on behavior for several reasons. First, it is an empirical fact that most psychoactive drugs produce more substantial changes in EEG sleep patterns than in waking brain waves. It has been hypothesized that drugs within pharmacologically equivalent classes, eg, sedative hypnotics, tricyclic antidepressants, or antipsychotic drugs, may produce effects that are qualitatively similar within classes but differ across classes. If there is already some evidence for this hypothesis. For example, benzodiazepines and barbiturates produce similar effects on both rapid eye movement (REM) and stage 4 sleep. Another example is that antidepressants (both monoamine oxidase inhibitors and tricyclic agents) reduce REM sleep to extremely low levels while leaving stage 4 intact or somewhat increased. Although investigations thus far have not been sufficiently systematic or exhaustively to allow firm conclusions to be drawn for any drug class, the hypothesis of pharmacologic specificity of sleep effects remains of considerable interest. (Drugs that produce the same behavioral effect sometimes do so through different mechanisms. For this reason, one might find occasional agents within a given psychopharmacologic class that produce effects on sleep different from those produced by the majority of its members. However, for the hypothesis to remain tenable, such atypical agents should not produce the qualitative patterns characteristic of drugs with opposing actions, eg, no analeptic should produce the effects characteristic of sedative-hypnotics.) If the hypothesis of pharmacologic specificity of sleep effects is confirmed, it would offer the possibility of a drug classification system based on human brain electrophysiology.

A second and perhaps the most common application of the sleep EEG in psychopharmacology thus far has been to study hypnotic efficacy. The therapeutic effects sought with hypnotics are changes in sleep itself: more rapid onset, decreased awakening, and increased total sleep time. Ideally, these improvements should be achieved without distortion of normal physiologic sleep patterns (although the functional importance of these patterns is still unknown). Sleep EEG records provide a continuous measure of brain activity that is closely correlated with behavioral sleep; and it is, of course, these recordings that define the normal electrophysiologic anatomy of human sleep. Several investigators have concluded, therefore, that the sleep EEG could define insomnia and measure the effectiveness of hypnotic drugs. This conclusion is premature. Many subjects who complain of insomnia show sleep patterns within normal limits, although with careful matching of insomniacs and controls, some differences can be detected.

One cannot doubt the importance of the insights into hypnotic effects contributed by EEG sleep studies, especially the demonstration of rapid habituation to the effects of these drugs on measures of arousal (sleep onset latency and awakenings). Nevertheless, to the degree that the correlation between sleep EEG patterns and the complaint of insomnia remains imperfect, insomnia must be consid-

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considered a symptom rather than a sign, and efficacy in its
treatment must be defined by subjective improvement
rather than electrophysiologic response.

A third source of interest in drug effects on sleep is that
they might shed light on pharmacokinetics. Whatever the
functional importance of the sleep EEG changes induced
by drugs, their substantial nature and relatively easy
measurement provide the opportunity to use them as
temporal markers, ie, as nonintrusive indexes of the time
required to affect brain function. Such an application
might furnish a useful supplement to other kinetic data,
such as plasma clearance rates.

Finally, drug effects on sleep can serve as tools to
investigate more basic issues. For example, drugs may be
used to modify the availability of specific neurotransmit-
ters in an attempt to determine their role in sleep
processes. In addition, drugs may be used to alter sleep
stage distributions and the behavioral significance of such
changes might be studied. Thus, the fact that monoamine
oxidase inhibitors can virtually eliminate REM sleep in
human subjects for prolonged periods without detrimental
effects on behavior raises questions regarding the func-
tional importance of the neuronal activity that occurs in
this state. The fact that stage 4 sleep is reduced by
flurazepam to a far greater extent than by barbiturates
without greater "hangover" or cognitive impairment
raises similar questions regarding this sleep stage.

In the present investigation, we applied computer tech-
niques to elucidate flurazepam effects on stage 4 EEG and
we used sleep cycle analysis to determine the time course
of the changes in visually scored stage 4 and REM sleep.
The reduction of stage 4 by flurazepam is of considerable
interest to those concerned with the psychobiologic impor-
tance of the different sleep stages since several facts
suggest that stage 4 sleep plays an important role in
human brain function: it is the sleep stage most closely
correlated with duration of previous wakefulness and
with age. Moreover, stage 4 is preserved or increased in
amount when total sleep time is artificially limited.

Visual scoring of stage 4 depends on the occurrence
within a given temporal epoch of a stipulated density of
delta waves that exceed an amplitude criterion. A change
in amount of visually scored stage 4, therefore, could result
from a reduction in any of the following: total number of
delta waves, delta wave distribution, or delta wave am-
plitude. Our method of computer analysis allowed evaluation
of these different possibilities.

In the present investigation, we studied the initial and
short-term effects of flurazepam hydrochloride on the
sleep patterns of four normal subjects. We evaluated the
effects of flurazepam on both visual sleep stages and
computer measures with a statistical technique ("protected
t test") that reduces the problems caused by multiple
tests of significance. Although such multiplicity is inevit-
able in drug studies that attempt to assess empirically
changes in sleep variables over several conditions, this
problem is rarely mentioned in the sleep literature. A
second advantage of the statistical analysis we used is that
it permitted calculation of the percentage of within-subject
variance accounted for by the experimental conditions.
These percentages more meaningfully indicate the relative
magnitude of the effects produced than do mean differ-
ences. A brief report of some of the findings reported
here has already appeared.

METHODS

Subjects

Subjects were four male medical students who ranged in age
from 22.6 to 25.5 years, with a mean age of 23.7 years. None
suffered from any sleep disturbance. All were in good health and
gave their informed consent after a full explanation of the
procedures.

Dosage and Recording Schedules

Sleep EEGs had been recorded during five consecutive baseline
nights two months earlier as part of a previous investigation.
Nights 2 to 4 provided the baseline values for the present study.
On all drug nights, flurazepam was administered about 15 minutes
before bedtime, which was held constant at 11 PM. On the first two
nights in the laboratory, the subjects received 15 mg and 30 mg of
flurazepam hydrochloride, respectively (initial drug). For the next
three nights, the subjects took 30 mg at home and retired at 11 PM.
They then returned to the laboratory for six consecutive nights of
recording—the first three nights taking 30 mg ("short-term"
drug), and the last three nights without any drug (withdrawal
condition). Thus, the subjects received 15 mg of flurazepam
hydrochloride on the first drug night and then 30 mg for seven
consecutive nights, followed by three withdrawal nights. Placebos
were not used in baseline or withdrawal conditions. There were
two considerations involved in this decision. The first was that we
knew large effects could occur. The second was that we believed it
was necessary that the subjects who were following their normal
daytime routines be aware of the possible dangers of drug
hangover and we did not wish to extend the restrictions on their
activities. However, sleep records were coded and scored without
knowledge ("single blind") of drug condition.

Data Recording

Sleep recording and visual sleep stage scoring were done
according to methods described previously. Electroencephalo-
grams were recorded on magnetic tape. The computer program we
used for the analysis of the sleep EEG is presented in detail
elsewhere.

Briefly, we visually identify non-REM (NREM), REM, and
waking stages on the basis of the polygraphic record. Segments of
FM-tape record identified by time code as corresponding to
NREM sleep are then subjected to period and amplitude analysis
with a minicomputer. Analysis is done by digital conversion,
waves are classified by duration into one of nine frequency bands.
For each band, four primary measures are obtained: integrated
amplitude, number of zero crossings, time spent in band, and
length of waves in band (curve length). Subsequent data process-
ing (on an IBM 370 system) computes six secondary measures
from the four primary variables and provides results as sums for
all NREM sleep, for each successive NREM period (NREM) and,
for the primary variables, for the average 20-second epoch of
NREM sleep.

RESULTS

Statistical Analysis

Both the computer-derived and visually scored measures
were analyzed with a multiple regression/correlation
procedure for repeated measures analysis of variance. The
advantages of these methods were described previ-
ously. Sleep data were compared across experimental condi-
tions using all-night and by-cycle values for the first four

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Table 1.—Mean Values for Visually Scored Sleep Measures in Baseline and Experimental Conditions.*

<table>
<thead>
<tr>
<th>Sleep Latency and Total Sleep Time</th>
<th>Baseline</th>
<th>Initial Drug</th>
<th>Short-term Drug</th>
<th>Withdrawal</th>
<th>% Within-S Variance Accounted for by Experimental Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep latency, min</td>
<td>16.6</td>
<td>13.3</td>
<td>9.7</td>
<td>9.31</td>
<td>15.4</td>
</tr>
<tr>
<td>Total sleep time, min</td>
<td>410.1</td>
<td>430.9†</td>
<td>431.8†</td>
<td>429.3†</td>
<td>23.2</td>
</tr>
<tr>
<td><strong>REM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye-movement (EM) latency, min</td>
<td>67.3</td>
<td>110.1†</td>
<td>100.2†</td>
<td>97.9†</td>
<td>26.4</td>
</tr>
<tr>
<td>Total stage REM, min</td>
<td>135.7</td>
<td>114.9†</td>
<td>106.7†</td>
<td>127.3</td>
<td>26.0</td>
</tr>
<tr>
<td>% stage REM (stage REM/total sleep time)</td>
<td>33.7</td>
<td>26.6†</td>
<td>24.8†</td>
<td>29.7</td>
<td>36.7</td>
</tr>
<tr>
<td>Total EMs (4-s epochs)</td>
<td>549.7</td>
<td>346.3†</td>
<td>290.3†</td>
<td>457.0</td>
<td>57.0</td>
</tr>
<tr>
<td>EM density (4-s epochs/stage REM (4-s epochs))</td>
<td>0.28</td>
<td>0.203†</td>
<td>0.188†</td>
<td>0.24†</td>
<td>37.0</td>
</tr>
<tr>
<td>Total EMs (4-s epochs)</td>
<td>0.09</td>
<td>0.055†</td>
<td>0.054†</td>
<td>0.071†</td>
<td>55.0</td>
</tr>
<tr>
<td>Burst index (EM44/EM30)</td>
<td>2.69</td>
<td>2.37†</td>
<td>2.33†</td>
<td>2.65†</td>
<td>34.9</td>
</tr>
<tr>
<td>Total NREM interruptions (20-s epochs) of REMPs</td>
<td>23.6</td>
<td>14.9†</td>
<td>12.8†</td>
<td>14.3†</td>
<td>24.5</td>
</tr>
<tr>
<td><strong>NREM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total NREM, min</td>
<td>274.4</td>
<td>316.0†</td>
<td>325.1†</td>
<td>302.0†</td>
<td>55.7</td>
</tr>
<tr>
<td>Mean duration of NREMP, min</td>
<td>60.3</td>
<td>78.5†</td>
<td>74.2†</td>
<td>70.6†</td>
<td>48.5</td>
</tr>
<tr>
<td>Total stage 4, min</td>
<td>35.2</td>
<td>32.2</td>
<td>6.41†</td>
<td>4.83†</td>
<td>58.0</td>
</tr>
<tr>
<td>% stage 4 (stage 4/NREM)</td>
<td>12.7</td>
<td>10.2</td>
<td>1.96†</td>
<td>1.73†</td>
<td>56.2</td>
</tr>
<tr>
<td>Total stage 3, min</td>
<td>59.1</td>
<td>62.1</td>
<td>50.2</td>
<td>53.4</td>
<td>11.7</td>
</tr>
<tr>
<td>% stage 3 (stage 3/NREM)</td>
<td>21.7</td>
<td>19.7</td>
<td>15.61†</td>
<td>17.9†</td>
<td>21.8</td>
</tr>
<tr>
<td>Total stage 2, min</td>
<td>180.1</td>
<td>221.6†</td>
<td>268.6†</td>
<td>243.7†</td>
<td>65.1</td>
</tr>
<tr>
<td>% stage 2 (stage 2/NREM)</td>
<td>65.8</td>
<td>70.0†</td>
<td>82.5†</td>
<td>80.4†</td>
<td>59.8</td>
</tr>
</tbody>
</table>

*Significance levels of mean differences and proportions of variance accounted for by drug effects are given. Means are based on two nights in initial drug condition and three nights in each of the other conditions.

†Significantly different from baseline value at .05.
‡Significantly different from baseline value at .01.
§Significantly different from initial drug condition value at .05.
¶Significantly different from initial drug condition value at .01.
#Significantly different from initial drug condition value at .001.

NREMPs. For the cycle analyses, the linear and quadratic trends within nights were computed and changes across experimental conditions in these trends were tested for significance. (Shown in the appropriate table are P values for statistically significant differences mentioned in the text.) Table 1 gives the results for the visually scored sleep variables.

**Total Sleep Time and Sleep Latency.**—There were no significant differences in time in bed across conditions (mean for all conditions was 445.7 minutes). Total sleep time was significantly elevated above baseline in initial drug, short-term drug, and withdrawal conditions. Sleep latency fell from baseline to initial drug to short-term drug and withdrawal conditions. Only the difference between baseline and withdrawal was statistically significant; however, as noted previously, these were normal and not insomniac subjects. The increase in total sleep time resulted from an increase in NREM sleep: this increase consisted of stage 2 EEG and largely occurred in the first NREM of the night. The number of sleep cycles was unaffected by drug, i.e., total sleep time was increased by virtue of increased length, rather than number, of cycles.

**REM Sleep.**—Rapid eye movement latency, i.e., the first NREM, increased significantly after drug administration and remained elevated through short-term and withdrawal conditions. The duration and percentage of REM sleep were significantly depressed in initial drug and short-term drug conditions compared with both baseline and withdrawal conditions. There were no significant differences between the initial drug and short-term drug conditions or between the baseline and withdrawal conditions in REM duration. Our analysis of sleep cycles permitted us to determine the time course of these effects. The 15-mg dose, given on the first night, did not affect REM duration until the third cycle, and it produced a significant change.
in the trend of REMP durations across the night. The same result was found for the changes in eye movement (EM) activity (Fig 1). On the second night, when a 30-mg dose was given, all REMP values were lower than baseline but the trend of these values across the night did not differ from baseline. The difference between the two nights could have resulted from either a dose-specific effect (night 1) or a carry-over effect (night 2). Whichever the case, our data indicate that the induction time of the REM sleep effects of an initial 15-mg dose of flurazepam hydrochloride is about 5.3 hours (mean onset time of REMP, on the first drug night).

The number (total EM) and proportion (density) of four-second epochs of REM sleep containing EM activity were greatly reduced in both initial dose and short-term drug conditions compared with baseline and withdrawal values. Flurazepam also reduced the tendency for EM to occur in bursts and the ratio of EM activity to total sleep time. The effects on total EM accounted for a far greater proportion of within-subject variance (57%) than did effects on REM duration (28%). There were no significant differences in EM measures between the two drug conditions or between baseline and withdrawal. The linear and quadratic trends of EM measures across sleep cycles did not differ in baseline, short-term drug, and withdrawal conditions although, of course, the absolute levels did. This stability of within-night trends in the face of strong drug effects testifies to the fundamental nature of these temporal characteristics of sleep. Examination of EM values during the three withdrawal nights shows that return to baseline was not achieved until the third night. The time course of the drug effects on EM activity was strikingly different from that on stage 4 (see the following related section).

NREM Interruptions of REM Sleep.—The number of NREM interruptions of REM sleep (the number of epochs of REM sleep in which a spindle or K-complex occurred in the absence of EM) was significantly reduced below baseline in the three other conditions. It is not clear whether this unexpected change should be regarded as an effect on NREM or REM sleep (see "Comment").

Effects on NREM Sleep.—Non-REM duration increased significantly in initial dose and short-term drug conditions as compared with baseline. Most of this increase occurred in the first cycle. After withdrawal of flurazepam therapy, NREM duration returned toward, but remained significantly above, baseline levels. Non-REM duration did not differ significantly in the initial drug and short-term drug conditions.

Stage 4 duration was substantially reduced in short-term drug from baseline and initial drug levels. The stage 4 suppression persisted without significant change during withdrawal. While total stage 4 during the initial drug condition did not differ significantly from that in baseline, sleep cycle analysis revealed a major change in its distribution across the night. On the first initial dose night, the amount of stage 4 increased over baseline by 50% in the first cycle and decreased by 20% in the second cycle (Fig 2). This effect was not simply due to a lengthened first NREMP (increased "REM latency"), since the proportion as well as the absolute amount of stage 4 within NREMP was increased. A reduction in stage 4 by flurazepam requires several nights of administration to become apparent. However, the cycle analysis used here demonstrated an effect on stage 4 distribution early in the first night.

While most reports of flurazepam effects on sleep stages indicate that stage 2 EEG is increased, it is the decrease in stage 4 rather than the increase in stage 2 that is usually emphasized. As given in Table 1, the increase in stage 2 duration exceeded the combined reductions in stage 4 and REM duration and entirely accounted for the increase in total sleep time. Experimental effects on stage 2 accounted for 65.1% of the within-S variance, the highest proportion of any visually scored sleep variable.

There were no significant differences among conditions in amount of stage 3 summed over the entire night. However, the distribution of stage 3 across the night was different in initial drug, short-term drug, and withdrawal conditions from that of baseline (F = 8.11; P < .01). In both the drug and withdrawal conditions, stage 3 was increased in cycle 1 and decreased in cycle 2 as compared with baseline.

NREM-REM Relations.—When NREM and REM durations are considered jointly, one might infer that part of the increase in NREM sleep during drug conditions was "secondary" to the reduced REM duration. However, there also seemed to be a "primary" effect as well, since NREM sleep increased beyond the decrease in REM and since NREM sleep remained persistently elevated during with-

Fig 2.—Minutes of stage 4 in each sleep cycle plotted by drug condition. Data of two initial drug nights are plotted separately, and the mean figures across nights for other conditions are shown. First night (15 mg) of flurazepam administration leads to an increase in stage 4 in NREMP, and a decrease to very low levels in NREMP. Second night of administration shows a similar pattern but with stage 4 reduced almost to baseline levels in first cycle. This finding strikingly resembles the effects of secobarbital on stage 4 distribution. Density of stage 4 within NREMPs showed a similar pattern, indicating that increased stage 4 in NREMP, on initial administration was not simply the consequence of increased length of NREMP, associated with delayed REM.
Table 2.—Mean Values for Computer Measures of 0- to 3-Hz Activity During NREM Sleep.*

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Initial Drug</th>
<th>Short-term Drug</th>
<th>Withdrawal</th>
<th>% Within-S Variance Accounted for by Experimental Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of 20-s epochs of NREM sleep</td>
<td>810.6</td>
<td>940.11</td>
<td>973.41</td>
<td>894.41</td>
<td>56.9</td>
</tr>
<tr>
<td>Primary Measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sums for all NREM epochs per night:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) Integrated amplitude (μV × s) + 100</td>
<td>2,118.9</td>
<td>2,039.3</td>
<td>1,520.91 $^\dagger$</td>
<td>1,464.31 $^\parallel$</td>
<td>69.9</td>
</tr>
<tr>
<td>(2) Baseline crossings, No. + 10</td>
<td>3,090.4</td>
<td>3,505.5</td>
<td>2,942.41 $^\dagger$</td>
<td>2,737.81 $^\parallel$</td>
<td>41.5</td>
</tr>
<tr>
<td>(3) Time in band, s + 100</td>
<td>96.8</td>
<td>103.1</td>
<td>93.5</td>
<td>84.11 $^\parallel$</td>
<td>43.2</td>
</tr>
<tr>
<td>(4) Curve length, μV + 1,000</td>
<td>3,519.9</td>
<td>3,734.9</td>
<td>3,057.31 $^\dagger$</td>
<td>3,068.0 $^\parallel$</td>
<td>29.1</td>
</tr>
<tr>
<td>Values per 20-s epoch of NREM:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(5) Total integrated amplitude, μV × s</td>
<td>280.1</td>
<td>216.6 $^#$</td>
<td>156.31 $^|$</td>
<td>164.21 $^\parallel$</td>
<td>78.8</td>
</tr>
<tr>
<td>(6) Baseline crossings, No.</td>
<td>38.1</td>
<td>35.2 $^#$</td>
<td>30.21 $^|$</td>
<td>30.51 $^\parallel$</td>
<td>74.4</td>
</tr>
<tr>
<td>(7) Time in band, s</td>
<td>11.9</td>
<td>11.0</td>
<td>9.61 $^\parallel$</td>
<td>9.41 $^\parallel$</td>
<td>70.2</td>
</tr>
<tr>
<td>(8) Total curve length, μV</td>
<td>4,323.2</td>
<td>3,956.6</td>
<td>3,133.91 $^\parallel$</td>
<td>3,447.7 $^\parallel$</td>
<td>56.1</td>
</tr>
<tr>
<td>Secondary Measures**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(9) Average frequency weighted by time, Hz</td>
<td>1.61</td>
<td>1.61</td>
<td>1.60</td>
<td>1.64</td>
<td>28.1</td>
</tr>
<tr>
<td>(10) Frequency of average wave, Hz</td>
<td>1.83</td>
<td>1.84</td>
<td>1.85</td>
<td>1.86 $^\parallel$</td>
<td>42.6</td>
</tr>
<tr>
<td>(11) Average integrated amplitude per half wave, μV × s</td>
<td>6.8</td>
<td>6.2</td>
<td>5.21 $^\dagger$</td>
<td>5.41 $^\parallel$</td>
<td>56.9</td>
</tr>
<tr>
<td>(12) Average sample rectified amplitude, μV</td>
<td>21.5</td>
<td>19.7</td>
<td>16.31 $^\parallel$</td>
<td>17.51 $^\parallel$</td>
<td>67.5</td>
</tr>
<tr>
<td>(13) Average rectified slope, μV + s</td>
<td>363.8</td>
<td>362.8</td>
<td>335.9</td>
<td>381.8</td>
<td>8.4</td>
</tr>
<tr>
<td>(14) Average curve length per half wave, μV</td>
<td>113.1</td>
<td>112.5</td>
<td>104.6</td>
<td>117.7</td>
<td>8.0</td>
</tr>
</tbody>
</table>

*Significance levels of mean differences and proportions of variance accounted for by drug effects are listed. Means are based on two nights in the initial drug condition and three nights in each of the other conditions.

$^\dagger$Significantly different from baseline value at .001.

$^\parallel$Significantly different from baseline value at .01.

$^\|Significantly different from initial drug condition value at .01.

$^\#Significantly different from initial drug condition value at .001.

$^\#Significantly different from initial drug condition value at .05.

$^\#Significantly different from baseline value at .05.

**Variable 9 = variable 3 + 2 (variable 2); variable 10 is complex, and a description is obtainable from the authors; variable 11 = variable 1 + variable 2; variable 12 = variable 1 + variable 3; variable 13 = variable 4 + variable 3; variable 14 = variable 4 + variable 2; computed for all NREM per night.

drawal although REM duration had returned to baseline. The NREM augmentation was almost entirely in stage 2, in which the increase, being greater than the combined decrease in REM and stage 4 durations, produced an increase in total sleep time. We will discuss in the context of our computer analyses the importance we attach to the fact that the increase in stage 2 occurred in the first NREMP, which normally has the highest proportion of stage 4 sleep.

Measures of NREM interruptions of REM sleep have not been previously reported in studies of flurazepam effects. It was somewhat surprising (in view of the increase in amount of NREM sleep and of the fact that flurazepam stimulates sleep spindles14) that NREM interruptions decreased significantly during drug and withdrawal conditions. (As noted previously, occurrence of spindles or K-complexes in the absence of EM is the criterion for a NREM interruption of an epoch of REM sleep.) The reduction of NREM interruptions persisted during withdrawal, suggesting that this phenomenon reflects an alteration in NREM rather than REM mechanisms.

Possible effects of order of experimental conditions were not controlled in this experiment. Therefore, the question may be raised as to whether the changes in sleep stages we observed could have been due to adaptation to the laboratory. This is not a realistic possibility since the drug effects (decrease in both stage REM and stage 4) were both greater in magnitude and opposite in direction to those produced by adaptation.

Computer Measures of NREM Sleep

Total 0- to 3-Hz (Delta) Activity.—Table 2 gives the results of the computer analysis of delta wave activity during REM sleep. Of the four primary measures of total 0- to 3-Hz activity summed across all NREM sleep, only integrated amplitude was substantially reduced in the short-term drug condition, falling below baseline by 28% (P < .001). Drug effects accounted for 69.9% of within-S variance for this measure. In contrast, the number of waves and time occupied by waves in 0- to 3-Hz were not significantly reduced below baseline in the short-term drug condition. This finding was surprising in view of the major decrease (by 82%) of stage 4 in this condition. The explanation for this apparent paradox lies in the increased stage 2 sleep under the short-term drug condition. Whereas stage 2 manifested 0- to 3-Hz activity, which was less dense and of lower amplitude than that in stages 3 and 4, it nevertheless contributed substantially to this frequency band. (The fact that visually scored stage 2 contains a substantial amount of delta wave activity has also been demonstrated with Fourier analysis.21, 22) It was striking that the increased stage 2 in the short-term drug condition
compensated almost perfectly in number and duration of delta waves for the loss of 0- to 3-Hz activity in stage 4. This compensatory change occurred in NREM, which normally manifests extremely high levels of stage 4.

During withdrawal, integrated amplitude of 0- to 3-Hz activity remained significantly reduced. Total number and duration of these delta waves also decreased significantly below baseline. These latter changes were the result of the decline in total NREM (stage 2) sleep as REM duration returned to baseline levels, ie, the rate of delta wave production per 20-second epoch (see following related section) was the same during withdrawal as in the short-term drug condition. Although stage 2 decreased in withdrawal, it remained significantly above baseline so that the reductions in absolute number and duration of 0- to 3-Hz waves (11% and 13%), while highly significant, were small in comparison with the persistent and profound (86%) reduction of stage 4 in withdrawal.

0- to 3-Hz Density. Values of 0- to 3-Hz activity for the average 20-second epoch of NREM sleep reflect the density of delta waves. Since the same total number and duration of 0- to 3-Hz waves were distributed over a larger number of epochs, ie, increased total non-REM sleep, in the short-term drug condition as compared with baseline, the average levels for these measures declined significantly. Integrated amplitude, which manifested an absolute decrease when the subject was receiving the drug although total sleep time was increased, showed a greater reduction in density than the other measures. The density of delta wave activity was reduced below baseline in the short-term drug condition and remained essentially unchanged in withdrawal. The smallest change was shown by the curve length measure, which is subject to opposing effects by flurazepam, ie, curve length should be reduced when delta waves are smaller but augmented by the increased spindling and fast activity known to be produced by this drug.**

Secondary Measures of 0 to 3 Hz.--Secondary measures are derived from the primary measures.** This analysis revealed that the average frequency of waves within 0 to 3 Hz was unchanged in the short-term drug condition. Average frequency within the 0- to 3-Hz band is a remarkably stable individual characteristic, eg, two-night correlation \( r = .95; N = 20; P < .0001. **\) This stability permitted a rather slight increase over baseline (mean change was 0.05 Hz) in frequency of the average wave during withdrawal to reach a high level of statistical significance \( (P < .001). \) The reduction in integrated amplitude, with number and duration of 0- to 3-Hz waves unchanged, resulted in significant reductions of the average integrated amplitude/half wave and of the average sample amplitude in both short-term drug and withdrawal conditions.

**COMMENT**

This investigation yielded the following four new observations regarding flurazepam effects on sleep: (1) Suppression of stage 4 during drug administration does not entail a net loss in the number of delta waves or in the time occupied by this frequency band; however, total integrated amplitude per night within the delta band is reduced by about 25% as a result of a decrease in average wave amplitude. (2) Analysis of visually scored data by successive NREM/REM periods reveals that the distribution of visually scored stage 4 sleep is significantly altered by a single 15-mg dose of flurazepam hydrochloride, although total stage 4 is not decreased. (3) The REM suppression after an initial 15-mg dose of flurazepam hydrochloride becomes apparent in the third REM period in the night, ie, about 5.3 hours after drug administration. (4) Interruptions of stage REM by brief snatches of stage 2 sleep are reduced by flurazepam. In addition to these new findings, the recent evidence that benzodiazepines and barbiturates increase characteristic, raise the possibility that this sleep stage is of little functional importance. However, the results of the computer analyses are consistent with an alternative possibility. Stages 2, 3, and 4 of NREM sleep may represent increasing "intensities" or "rates" of the same qualitative process.** If this is true, a longer period of less intense (stage 2) sleep might substitute functionally for a shorter duration of more intense (stage 4) activity. Our finding that stage 2 sleep under flurazepam is increased in duration well beyond the decrease in stage 4 (47 vs 29 minutes) is consistent with this possibility. The increased stage 2 produced by this drug, while invariably statistically significant, has seldom received much emphasis. In the present study, flurazepam administration accounted for a higher proportion of the within-subject variance for stage 2 sleep than for any other visually scored sleep variable.

The computer analysis also provided data consistent with the hypothesis that increased stage 2 EEG compensates for what is lost with stage 4 suppression by flurazepam. This analysis demonstrates that the increased stage 2 duration provided precisely the number and duration of delta waves required to maintain these measures at baseline levels. Moreover, this "compensation" did not occur simply by "tackling on" more sleep at the end of the night but all of the increase in stage 2 occurred in the first NREMP, which normally contains more than 50% of the night's stage 4.**

If the interpretation regarding the relation of stages 2 and 4 is correct, it holds a more fundamental implication regarding the mechanism by which hypnotics increase total sleep time: this increase may be achieved by a slowing of the metabolic activity that underlies the sleep EEG. This interpretation is consistent with current evidence that sleep is an active process and also with the fact that hypnotics depress neuronal function, reducing brain oxygen uptake and causing coma in higher dosages. Of course, hypnotics possess other effects as well. They decrease arousal level, reducing the time required for sleep onset, and they diminish the number of nocturnal awakenings. The recent evidence that benzodiazepines and barbiturates increase characteristically different time courses. Rapid eye movement suppression is immediate but dissipates quickly during withdrawal; stage 4 suppression is delayed and persists unchanged over a three-day withdrawal period.

In what follows, we comment briefly on each of these issues.

As noted in the beginning of this article, the profound suppression of stage 4 EEG by flurazepam, which is unaccompanied by substantial behavioral or cognitive impairment, raises the possibility that this sleep stage is of little functional importance. However, the results of the computer analyses are consistent with an alternative possibility. Stages 2, 3, and 4 of NREM sleep may represent increasing "intensities" or "rates" of the same qualitative process.** If this is true, a longer period of less intense (stage 2) sleep might substitute functionally for a shorter duration of more intense (stage 4) activity. Our finding that stage 2 sleep under flurazepam is increased in duration well beyond the decrease in stage 4 (47 vs 29 minutes) is consistent with this possibility. The increased stage 2 produced by this drug, while invariably statistically significant, has seldom received much emphasis. In the present study, flurazepam administration accounted for a higher proportion of the within-subject variance for stage 2 sleep than for any other visually scored sleep variable.

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increase sigma spindles (bursts of 12- to 14-Hz waves characteristic of human sleep) also raises the possibility that they directly stimulate sleep control mechanisms; we hypothesize that sleep spindles are correlated with the control processes of sleep rather than with its restorative functions.

Although there is no net loss of delta waves in subjects taking flurazepam, there does occur a decline in the amplitude of the average wave. Benzodiazepine suppression of delta amplitude during sleep has been demonstrated with computer techniques by other investigators as has the reduction in delta wave density.33-35 However, we are not aware of any previous analysis that simultaneously measured NREM sleep all of the delta variables included in this study, ie, number, duration, amplitude, and density.

The functional importance of the changes in delta amplitude and density induced by flurazepam are not apparent. One possibility is that such changes might be related to degree of drug-induced "hangover." Obviously, it would be of considerable practical value to establish physiologic correlates of hangover. However, in addition to the effects on delta amplitude and distribution, sleep EEG changes suggest several additional candidates, including stage REM and EM suppression and spindle and beta wave stimulation. In addition to examining the relation of these changes to the toxic effects or side effects of the drug, one might seek to determine whether they are correlated with particular pharmacologic actions, such as anticonvulsant or hypnotic efficacy. Dumerum and other investigators3 on the basis of findings with the waking EEG, suggested that the capacity to stimulate beta activity may be correlated with anticonvulsant effectiveness. However, on an a priori basis, the same possibility exists for each of the sleep EEG changes produced by flurazepam, taken together. Studies of these potential relations might advance our understanding of hypnotic mechanisms.

The changed distribution of stage 4 after administration of a single 15-mg dose of flurazepam hydrochloride has not to our knowledge been previously reported. The immediate interest of this finding is that it strikingly resembles the change in stage 4 EEG observed by Lester et al.3 after a single 200-mg dose of secobarbital. These investigators, analyzing stage 4 by hour of the night rather than by NREM period, found that secobarbital increased stage 4 in the first two hours and decreased it subsequently. Thus, in addition to the similarity of their effects on total stage REM and stage 4, barbiturates and benzodiazepines produce identical initial effects on stage 4 distribution.

Examination of the temporal pattern of sleep also enabled us to detect the onset of flurazepam suppression of REM activity. This effect became apparent in the third REM period (about 5.8 hours after sleep onset) of the first night. It seems plausible that the interval between drug administration and sleep stage effects could serve as an absolute limit of the time required for psychoactive drugs to penetrate the blood-brain barrier and to exert effects on neuronal function.

Thus, the induction time, as well as the persistence of effects after withdrawal, differ for the REM and stage 4 suppression produced by flurazepam. These differences merit greater attention than they have received. They raise the possibility that the drug affects more than one receptor and thus may have differential affinities for, or quantitatively different metabolic effects on, the neurophysiologic systems governing the two kinds of sleep. Alternatively, there may be an effect on both one sleep system (REM or NREM) that induces interaction effects on the other.

A fourth effect of flurazepam (that to our knowledge is being reported here for the first time) was a reduction in the number of interruptions of REM sleep by NREM activity. Specifically, our measure of "NREM interruptions" represents the number of 20-second epochs within stage REM that contain spindles or K-complexes in the absence of EM. On its face, this change could result from alteration in either REM or NREM systems. The temporal course of this change may suggest the answer to this question. Whereas no REM measure during withdrawal differed significantly from its corresponding value in the baseline condition, every NREM measure did, except for stage 3. Since NREM interruptions remained significantly below baseline during the three-night withdrawal period, we suggest that the reduction in NREM interruptions represents an effect on NREM rather than REM systems.

The same logic could be applied to decide whether the change in REM latency, ie, the duration of the first NREM, produced by flurazepam is a NREM or REM effect. We have long emphasized the equivocal meaning of changes in this measure.40 In the present investigation, we found that REM latency remained significantly increased during withdrawal; as noted previously, changes which persisted during flurazepam withdrawal were characteristic of NREM rather than REM measures. The persistent increase of REM latency during withdrawal, therefore, supports the view that this measure—the amount of NREM sleep that precedes the first REM period—reflects the state of NREM systems rather than secondary to variations in "REM pressure."

Finally, the similarity of flurazepam effects on REM sleep to those produced by barbiturates merits emphasis in view of the persistent misapprehension that flurazepam does not suppress REM sleep. Here, we confirm previous reports of REM sleep reduction and EM suppression by flurazepam. The effect on EM is substantial (47%), unequivocal (P .001), and about twice as large as that on REM duration (52% vs 28% of variance). As with barbiturates, it is not clear whether this effect on EM activity represents a primary effect on sleep mechanisms or a depression of oculomotor excitability that simply becomes apparent during sleep.41 This interesting question can best be pursued on the level of basic neurophysiology.
References


CORRECTION

Error in Table.—In the article titled "Life Events and Prisoners," published in the February Archives (35:197-205, 1979) an error has occurred in Table 2. The life event "Death of spouse" has been incorrectly ranked for the middle-class group. The frequency should be 0.4 and the rank should be 36.5. This change in the rank ordering includes the subtraction of one point in rank from rank item 10 through rank items 35.5. The "Death of spouse" item shares rank 36.5 with item 37. Thus, from "Life Event" "Personal injury or illness" through to "Foreclosure of mortgage or loan" the entries under rank for the white middle-class group should read as follows: 7.5; 36.5; 7.5; 9; 10; 11.5; 11.5; 13.5; 13.5; 15.5; 15.5; 17.5; 17.5; 20; 20; 22; 23; 24; 25.5; 25.5; 27; 28; 29.5; 29.5; 31; 32.5; 32.5; 34.5; 34.5; and 36.5.

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