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Sleep Extension, Enhanced Alertness and the Sedating Effects of Ethanol

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ROEHRS, T., A. ZWYGHUIZEN-DOORENBOS, V. TIMMS, F. ZORICK AND T. ROTH. *Sleep extension, enhanced alertness and the sedating effects of ethanol.* PHARMACOL BIOCHEM BEHAV **34**(2) 321–324, 1989.—Twelve, healthy young men (mean age 25.6 years) consumed either ethanol (0.75 g/kg producing a peak breath ethanol concentration, BEC, of 0.060% on average) or placebo at 0900–0930 hr after spending 8 hr time-in-bed (TIB) the previous night and once again after 7 or 8 consecutive nights of 10 hr TIB. Latency to sleep onset (on the Multiple Sleep Latency Test, a standard measure of daytime sleepiness/alertness) was tested at 1000, 1200, 1400 and 1600 hr and divided attention performance was assessed at 1100 hr. Ethanol reduced sleep latency and divided attention performance and the sleep extension improved both sleep latency and divided attention performance. Sleep extension attenuated the sedating effects of ethanol; sleep latency after extending sleep did not differ between placebo and ethanol. While the effects of ethanol on performance still were detectable after sleep extension, the level of performance was at the 8-hr TIB placebo level. BEC peak and decline (determined before each latency test) did not change with the sleep extension. Hence, reduced BECs do not account for the reduction in the disruptive effects of ethanol with sleep extension.

Ethanol Sleepiness Performance MSLT

MANY are familiar with the reduced alertness and functioning that occurs daily over the midday (1200–1400 hr), that accompanies rapid travel across time zones ("jet lag"), or that a person experiences in shift work and night work. Scientific investigation of sleepiness and alertness (they are used as antonyms) has been facilitated by the recent development of sensitive and precise methods to measure sleepiness/alertness. The Multiple Sleep Latency Test (MSLT) assesses a person's latency to polygraphic signs of sleep in repeated opportunities at 2-hr intervals across the day (1). The procedure assumes that a sleepy person will go to sleep more quickly than an alert person and studies of its validity in a variety of experimental and clinical conditions have shown that to be true (4,11).

Among factors known to alter daytime sleepiness/alertness is the amount of prior sleep and wakefulness. Restriction of the usual 8 hr time in bed (TIB) produces increased sleepiness and extension of TIB by as little as 2 hours produces increased alertness (2). Furthermore, these restriction and extension effects accumulate over successive nights. Studies also have shown that some drugs affect daytime sleepiness/alertness. Long-acting benzodiazepines taken at bedtime produce increased sleepiness the following day, while short-acting ones do not (10). H_1 antihistamines which readily cross the blood-brain barrier also have been shown to objectively increase sleepiness during the day (9).

Ethanol also has sedating effects. It hastens sleep onset when taken at bedtime (6) and it recently has been shown to increase daytime sleepiness as measured by the MSLT (5). In fact, the disruptive effects of ethanol on daytime functioning may be, in part, related to its sedating effect. Furthermore, the sedating effect of ethanol and hence its potentially disruptive effect on performance is enhanced by increasing one's basal level of daytime sleepiness (13). After restricted sleep (5-hr TIB) a moderate amount of ethanol (0.4 g/kg) produced daytime sleepiness similar to that of a high dose (0.8 g/kg) after normal sleep (8 hr TIB).

A provocative question is whether the sedating and performance disruptive effects of ethanol can be diminished or even reversed by increasing one's basal level of daytime alertness. Given that previous studies have shown that extending TIB by several hours each night produces an increase in daytime alertness, this study compared the effects of ethanol before and after 7–8 nights of extended TIB.

METHOD

Subjects

Twelve healthy, young men, aged 21–34 years, who reported

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drinking between 1 and 12 alcoholic drinks per week were studied. Each had a physical examination, laboratory tests, and a nocturnal (2300–0700 hr) sleep recording followed the next day by a MSLT conducted according to standard procedures (3). Screening requirements are described below. Each signed an informed consent and was paid for participation.

Procedure

In a telephone screen each subject reported averaging 6.5–8 hr of sleep a night, regular bedtimes and times of arising, no difficulty sleeping, and no daytime napping. They also reported no use of psychoactive drugs, both licit and illicit. They then received a physical examination and standard laboratory tests with the results all within normal limits. A drug screen of urine samples was used to confirm the absence of psychoactive drugs.

In both the nocturnal sleep and daytime sleepiness screening, electrodes were attached for standard monitoring and sleep stage scoring (in 30-sec epochs) of tracings derived from monopolar EEG (at central and occipital placements), electrooculogram from right and left outer canthi, and chin electromyogram from the submental muscle (8). On these screening tests subjects had sleep efficiencies (sleep time per TIB) of greater than 85% and a mean sleep latency (on the MSLT) the following day of $\geq$16 min. Healthy normal adults on such a screening usually have MSLT latencies of 10–15 min on average (4). Alert subjects were chosen for the present study since a previous study had demonstrated the sedating effects of ethanol in sleepy individuals and the purpose of this study was to assess whether enhanced alertness could alter the sedating effects of ethanol (13).

Subjects consumed ethanol (0.75 g/kg) or placebo, presented in a counterbalanced order, on each of two mornings (0900–0930 hr) after 8 hr TIB and again after 7 or 8 consecutive nights of 10 hr TIB. The ethanol used was 80 proof vodka, mixed 1:4 with tonic water, and flavored with lemon or lime juice. The placebo consisted of the flavored tonic water with three drops of ethanol floating on the surface. The ethanol consumption was done in a nonsocial environment and drinking was paced over the 30-min period. Breath ethanol concentration (BEC) was measured (Alcotest 7010, National Draeger) each day at 1000, 1200, 1400, and 1600 hr prior to the sleep latency tests.

The bedtimes for the 8-hr and 10-hr TIBs were adjusted so as to maintain a constant 0700 hr arising time. Each morning after arising, bathing, and a breakfast of one roll with a glass of juice, subjects consumed the appropriate beverage (0900–0930 hr). They then received the MSLT at 1000, 1200, 1400, and 1600 hr and at 1100 hr divided attention performance was assessed. The divided attention task consisted of tracking a moving target which appeared on a video screen with a joystick (preferred hand), while responding on a response key (nonpreferred hand) when a stimulus appeared in the center or periphery of the tracking field. This type of task has been shown to be sensitive to the effects of ethanol and has face validity to those skills required in automobile driving (7). Subjects were trained on the divided attention task prior to administration of ethanol or placebo and there were no differences in the final training levels and the placebo levels of performance.

The dependent measures, sleep latency (min) on each latency test, BEC at each determination, and four divided attention performance measures were each submitted to two- or three-factor (TIB, ethanol, and time where appropriate) analyses using the general linear models multivariate analysis of variance (SAS Institute) followed by Duncan post hoc comparisons where appropriate. Conservative p levels corrected by the Greenhouse-Geisser procedure were used and effects of $p<0.05$ or less are reported.

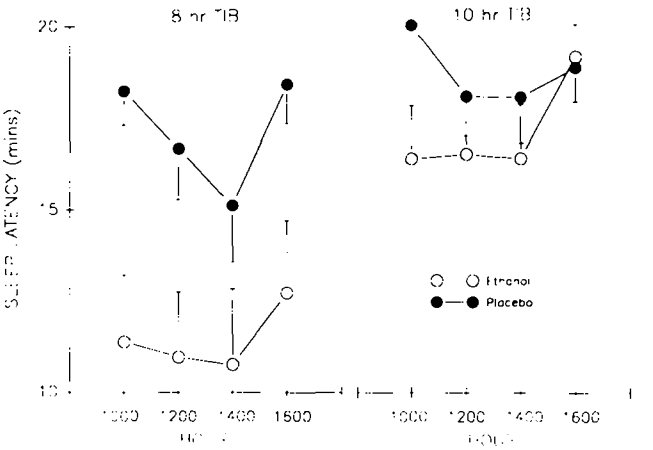

FIG. 1. Daytime sleep latency (min) at 1000, 1200, 1400 and 1600 hr after 8-hr TIB or 10-hr TIB the previous night and administration of placebo or 0.75 g/kg ethanol in the morning (0900–0930 hr). An ANOVA (TIB, ethanol, and time) revealed effects of TIB ($F=25.31$, $p<0.001$), ethanol ($F=24.95$, $p<0.001$), and a TIB by ethanol interaction ($F=17.98$, $p<0.001$).

RESULTS

Figure 1 presents sleep latency on each test during the day after an 8-hr TIB and a 10-hr TIB and after consuming ethanol (0.75 g/kg) or placebo at 0900–0930 hr. Ethanol significantly shortened sleep latency ($F=24.95$, $p<0.001$). After an 8-hr TIB mean sleep latency was reduced from 17.5 ± 2.5 min to 10.6 ± 4.8 min. Latency on each test was reduced by approximately 30% compared to placebo (see Fig. 1). There were no time of test (i.e., 1000 vs. 1200 hr) effects or interactions with time of test, although in the placebo condition the 1400 hr test latency reaches an apparent nadir.

Main effects of extending TIB also were observed. Sleep latency on each test increased a small, but consistent, amount as a result of the extended TIB ($F=25.31$, $p<0.001$). Mean daily sleep latency increased from 17.1 ± 2.5 min to 18.7 ± 1.8 min on the placebo day. See Fig. 1 to compare latencies on each test after the 8-hr and 10-hr TIBs.

There also was an interaction between sleep extension and the sedating effects of ethanol ($F=17.98$, $p<0.001$). The post hoc tests ($p<0.05$) indicated that after the 8-hr TIB sleep latency was reduced by ethanol relative to placebo, while after the sleep extension ethanol no longer significantly affected sleep latency (see Fig. 1). This diminution of the effects of ethanol with sleep extension occurred on each latency test; there were no time of test effects or interactions.

The divided attention performance measures are presented in Table 1. Divided attention performance showed ethanol-related impairments compared to placebo. The central reaction time was increased ($F=8.44$, $p<0.02$), the two measures of tracking deviations were increased ($F=8.90$, $p<0.01$; $F=12.66$, $p<0.01$) and overall divided attention performance (a combination of the four measures) expressed as z scores was impaired ($F=9.56$, $p<0.01$).

Performance on the divided attention task was improved after the extended TIB (see Table 1). Central and peripheral reaction times were reduced ($F=8.41$, $p<0.02$; $F=4.75$, $p<0.05$), average tracking deviations were reduced ($F=5.55$, $p<0.04$), and overall divided attention performance expressed as a z score was improved ($F=9.56$, $p<0.01$). However, unlike the MSLT, the effect of ethanol on performance remained after the 10-hr TIB (no

TABLE 1

DIVIDED ATTENTION PERFORMANCE

	8 hr TIB		10 hr TIB	
	Plac	Etoh	Plac	Etoh
Central RT*	24.33	25.25	23.22	23.80
	(3.96)	(3.57)	(4.60)	(2.97)
Peripheral RT†	25.33	26.92	24.11	25.00
	(4.12)	(3.53)	(3.76)	(3.13)
Avg Tracking Dev‡	78.58	84.33	75.22	77.00
	(8.16)	(9.31)	(6.08)	(7.70)
Sqd Tracking Dev§	134.4	483.3	152.7	196.6
	(28.8)	(50.3)	(45.5)	(43.8)
Div Atten z Score¶	−0.60	0.33	−1.37	−0.90
	(2.24)	(2.18)	(2.32)	(1.81)

Data are means and (standard deviations).

Measures are expressed in arbitrary computer generated units.

For all measures lower scores indicate improved performance.

*Extension ($F = 8.41$, $p<0.02$) and ethanol ($F = 8.44$, $p<0.02$) effects; †extension ($F = 4.75$, $p<0.05$) effects only; ‡extension ($F = 5.55$, $p<0.04$) and ethanol ($F = 8.90$, $p<0.01$) effects; §ethanol ($F = 12.66$, $p<0.01$) effects only; ¶extension ($F = 9.56$, $p<0.01$) and ethanol ($F = 7.88$, $p<0.02$) effects.

interactions were found). Yet, the absolute levels of performance were much improved. All divided attention measures after sleep extension and ethanol consumption were at a level similar to that of placebo before the sleep extension.

These changes in ethanol's effects are not the result of changes in BEC between the two administrations before and after the sleep extension. Table 2 presents BEC for each determination on each day of ethanol administration. BEC was 0.060% at 1000 hr, 30 min after consumption, and it declined steadily reaching zero at 1600 hr, 6.5 hr after ethanol consumption. The peak level and decline in BEC did not differ between the two administrations of ethanol (pre- and postsleep extension); there were no main effects of administration and no interactions. However, there were main effects of time of test ($F = 395.44$, $p<0.001$). The post hoc tests showed differences ($p<0.05$) in BEC between each successive bihourly determination. As reflected by the homogeneity of variances seen in Table 2, there was little variability among subjects in peak BEC and its decline.

TABLE 2

BREATH ETHANOL CONCENTRATION (%)

	8 hr TIB	10 hr TIB
1000 hr	0.060	0.060
	(0.01)	(0.01)
1200 hr	0.050	0.050
	(0.01)	(0.01)
1400 hr	0.020	0.020
	(0.01)	(0.01)
1600 hr	0.000	0.000
	(0.00)	(0.00)

Data are means and (standard deviations).

An ANOVA (TIB and time) showed a main effect of time ($F = 395.44$, $p<0.001$), but not TIB. Post hocs showed 1000 hr > 1200 hr > 1400 hr > 1600 hr.

DISCUSSION

The results of this study show that the sedating and performance disruptive effects of ethanol are attenuated when the basal level of sleepiness/alertness is increased by a small amount when extending TIB. These results compliment those of an earlier study in which the disruptive effects of ethanol were enhanced by increasing sleepiness as a result of reducing TIB for a series of nights (13). The present study and the earlier study clearly demonstrated that the alterations in the effects of ethanol are not due to changes in the pharmacokinetics of ethanol. BEC peak and decline did not change with sleep restriction or sleep extension.

Several points of interpretive caution regarding the results of this study must be made. First, the absence of ethanol effects on sleep latency after the 10-hr TIB seems to suggest that those effects were completely blocked by the enhanced alertness resulting from the sleep extension. But whether or not the sedating effects of ethanol were blocked by the extended TIB can not be determined from this study. Placebo levels of alertness after the extension were at the ceiling of the MSLT (a latency of 20 min) and consequently the absence of ethanol effects could be the result of an artificially reduced placebo level. Hence, we have interpreted the results as only indicating a diminution of ethanol effects and not a total reversal.

The performance data also must be interpreted cautiously. A differential effect of ethanol before and after sleep extension was not found (i.e., no interactions were seen). Given that we chose not to include a nonextension group and differential effects were not found, the performance improvements could be attributed to practice effects and not necessarily the enhanced alertness observed in this study. However, a number of completely controlled studies have previously shown that extending TIB improves performance (4). Furthermore, in this study, we included training sessions before the baseline assessment and found no difference between the final training level and the baseline 8-hr TIB levels of performance.

One interesting finding of this study relates to the observation of a continued sedation after BEC was zero. Whether and if so how this continued sedation relates to "hangover" is not clear. "Hangover" effects of ethanol, that is, impaired performance after ethanol is no longer detectable in breath or blood, have been reported. Fourteen hours after consuming enough ethanol to produce 100 mg% blood ethanol concentrations performance was impaired compared to placebo, although at that point blood ethanol concentration was zero (12). In this study, 6.5 hr after ethanol consumption in the 8-hr TIB condition, increased sleepiness relative to placebo was observed at 1600 hr when BEC was zero (see Fig. 1). This result replicates a previous study from this laboratory of the sedating effects of ethanol after an 8-hr or 5-hr TIB (13). In that study a similar continuation of sedation after BEC reached zero was reported. An important finding of the present study is that sleep extension completely reversed effects of ethanol and consequently no continued sleepiness was present as well. After sleep extension sleep latency at 1600 hr, 6.5 hr postethanol, was the same as that of placebo.

It is interesting that effects of ethanol after the sleep extension were still detectable on the performance measures but not on the MSLT. As noted earlier, this difference may be an artifact of the ceiling of the MSLT (i.e., placebo scores were at the MSLT ceiling). On the other hand, if the difference is real, it could reflect the fact that enhanced alertness protects only some of the skills

(i.e., attentional) necessary to perform a divided attention task against ethanol disruption, while other of the skills (i.e., motor) remain disrupted. A further careful analysis of the components of divided attention performance, sedation, and ethanol effects will be necessary to answer this question.

At this point in our understanding of the neurochemistry of sleepiness/alertness, one can only speculate regarding what changes in the brain occur as a result of extending TIB and hence increasing alertness or reducing sleepiness. Whatever those changes may be, they alter the usual central depressant effects of ethanol. Whether these results can be extended to other drugs with depressant effects has yet to be determined. There is literature on chronopharmacology which suggests that these results will in fact extend to other depressants. The presence of a circadian rhythm in sleepiness/alertness is well established (11). The fact that a time of day (circadian) effect or interaction was not found in this study probably relates to the select nature of the subjects (more alert) and the size of the "n" relative to variability. However, given that there is a circadian rhythm in sleepiness/alertness in most unselected populations, in part, chronopharmacologic effects may be due to circadian variations in sleepiness/alertness.

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