Circadian Variation of Ethanol Metabolism in Alcoholics*

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Summary

The rate of ethanol metabolism was determined for 20 alcoholics during afternoon and evening drinking sessions on two consecutive days. Alcoholics demonstrated a faster rate of ethanol metabolism in the evening as compared to the afternoon, suggesting a circadian variation in the rate of ethanol metabolism. Previous drinking on the first day appeared to increase the rate of ethanol metabolism on the second drinking day. This circadian variation of ethanol metabolism, which was present following two weeks of abstinence and one day of heavy drinking, is different from that reported for non-alcoholics. This suggests that other circadian rhythms may be affected in alcoholics, even after they have been dried out for several weeks. Altered circadian rhythms may partially explain the alcoholics' difficulty in re-adjusting to social demands.

Introduction

Social drinkers have been reported to demonstrate a circadian variation in the rate of ethanol metabolism (Wilson, Newman and Newman, 1956; Jones, 1973b). Wilson et al. (1956) reported that the rate of ethanol metabolism was slower during the night than during the day, with the slowest rate of metabolism occurring during sleep. Jones (1973b) also reported that social drinkers tested on a cognitive task in the evening had significantly slower ethanol elimination rates than social drinkers tested in the afternoon. Alcoholics also may demonstrate a circadian variation in the rate of ethanol metabolism. However, alcoholics may have a different circadian variation of ethanol metabolism since they often drink throughout the 24-hour day while social drinkers usually limit their drinking to the evening hours. For example, alcoholics may metabolize ethanol faster in the evening than in the afternoon as suggested by the data reported by Mello and Mendelson (1971). It also has been reported that length of abstinence is related to the rate of ethanol metabolism in alcoholics; the longer the length of abstinence, the slower the metabolism (Urgarte, Pereda, Pino and Iturriaga, 1972). This suggests that the circadian variation of ethanol metabolism should be evaluated in alcoholics after a non-drinking period as well as after a drinking period in order to determine if possible circadian effects are related to length of abstinence. It would also be important to determine if basic liver function is related to the circadian variation of ethanol metabolism or other ethanol variables. The present study is directed at determining possible circadian variation in rate of ethanol metabolism in alcoholics after they have been dry for several weeks and also after they have been drinking.

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Method

Subjects. Twenty alcoholic patients participating in a 5-week alcoholic treatment program served as subjects. Every two weeks an alcoholic was randomly selected to receive alcohol. Detailed information on the treatment program is presented elsewhere (Paredes, Hood, Seymour and Gollob, 1973).

Alcohol Beverage. The beverage consisted of 95 per cent USP ethanol mixed with ginger ale in a ratio of one part ethanol to four parts ginger ale. Drinks were offered to the subjects from 1.00 p.m. to 9.00 p.m. on two consecutive days. Beginning at 1.00 p.m. following lunch, the subject had the option of drinking one or two drinks during the coming hour that consisted of 20 milliliters of ethanol. All subjects chose the two drinks. The alcoholic was given his drink every 30 minutes. Breathalyzer samples were taken every hour beginning at 2.00 p.m. to obtain an estimate of blood alcohol level. The first breath sample was obtained after the patient consumed the drinks at 1.00 and 1.30 p.m., but before the 2.00 p.m. drink. The breaths were obtained from 15 to 30 minutes following the last drink. This procedure was followed throughout the testing sessions. Once a blood alcohol level of 0.10 per cent was reached, drinks continued to be offered but the amount of alcohol in each drink was decreased in order to allow the subject to continue drinking until he reached a blood alcohol level of about 0.15 per cent at bedtime. Patients ate dinner from 5.00 to 6.00 p.m. and then continued to drink until 9.00 p.m., at which time beverages ceased to be offered. The patient drank alone in a small room furnished with an easy chair. A research assistant monitored the procedure in an adjacent room. Electroencephalographic sleep recordings and other physiological measures were obtained from the subject on the nights after drinking had been discontinued and during the nights preceding and following the two days of scheduled drinking. These data are reported elsewhere (Lester, Rundell, Cowen and Williams, 1972).

Metabolic Rate. The measure of the rate of ethanol metabolism was similar to that reported by Wilson et al. (1956). They administered whiskey orally by giving repeated small doses of alcohol in order to achieve a slowly rising blood alcohol level. A predetermined dose of alcohol for each subject was given hourly. Their measure of ethanol metabolism was the rate of increase of the blood alcohol level each hour. A fast rate of blood alcohol level increase reflected a slow rate of metabolism while a slow increase reflected a fast rate of metabolism. This measure of ethanol metabolism allows the subject to consume large amounts of alcohol over a long period of time, thus reflecting the usual drinking pattern of an individual. This is in contrast to many other studies that require the subject to drink a large amount of alcohol in a short period of time (15 to 60 minutes) (Jones and Vega, 1972; Jones, 1973a) or rapidly inject alcohol intravenously (Ugarte et al., 1972) and then measure the rate of ethanol metabolism as the blood alcohol level declines over several hours. Although this latter measure may be a "purer" way of determining the rate of ethanol metabolism, it may also induce many other physiological systems and behavioral alterations as a consequence of a large volume of alcohol being rapidly dumped into the system.

The method of measuring the rate of ethanol metabolism in the present study was to determine the amount of increase of the blood alcohol level per milliliter of ethanol consumed each hour since subjects did not drink a constant amount of
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ethanol every hour. To determine ethanol metabolism in the afternoon, a regression equation was calculated for each patient using the milliliters of alcohol he consumed and the blood alcohol level he obtained at each hour from 2.00 p.m. to 5.00 p.m. A second regression equation was calculated from 6.00 p.m. to 9.00 p.m. to determine the evening value. These two equations yielded beta values indicating the amount of increase in blood alcohol level per milliliter of ethanol consumed. A high value indicated that alcohol was being absorbed rapidly but not metabolized quickly while a low value indicated that the blood alcohol level was not increasing rapidly and thus reflected a fast rate of ethanol metabolism. The difference in rate of increase of blood alcohol level over time was compared between afternoon and evening to determine if rate of ethanol metabolism was different for these two times.

Dry vs Drinking Condition. In order to determine if the rate of ethanol metabolism was related to the prior condition of the subject in relation to alcohol intake, each subject was tested after being dry for two weeks (Day 1) and also the day after the first controlled drinking (Day 2). Differences between the rate of metabolism on these two days would indicate if the alcoholic metabolizes ethanol differently when he is dry than when he has been drinking.

Liver Function. Serum glutamic—oxaloacetic transaminase (SGOT) and alkaline phosphatase values were obtained for each subject prior to the scheduled drinking periods. No subject with cirrhosis of the liver was admitted into the treatment program so most values fell within an acceptable normal range. The 20 alcoholics were ranked on SGOT values and then divided at the median value to determine if liver function was related to amount of alcohol consumed or any of the blood alcohol variables. Group I consisted of the 10 alcoholics with low SGOT values and Group II consisted of the 10 alcoholics with high SGOT values.

Data Analysis. A 2 x 2 x 2 factorial analysis of variance with repeated measures on the last two factors was carried out to evaluate the relationship of liver function, wet versus dry prior condition and afternoon versus evening testing to the rate of ethanol metabolism.

Results

Means and standard deviations for the SGOT values for Group I and Group II respectively were 21.30 ± 5.70 (range 14–28) and 75.13 ± 48.22 (range 32–164) (t = 3.14, p < 0.01). Group I also had significantly lower alkaline phosphatase levels than Group II (t = 3.11, p < 0.01). Group I and Group II were not significantly different on age (37.80 ± 10.40 and 38.70 ± 9.00, respectively) or years of heavy drinking (11.50 ± 5.40 and 10.00 ± 6.70, respectively).

Blood Alcohol Variables. Means and standard deviations for body weight, amount of ethanol consumed, dose of ethanol and peak blood alcohol level on Day 1 and Day 2 for Group I and Group II are presented in Table 1. There was no significant difference between Group I and Group II for body weight, or for ethanol consumed or dose for either Day 1 or Day 2. However, Group II did achieve a significantly higher peak blood alcohol level than Group I on Day 1 (t = 3.02, p < 0.01) but not on Day 2. This indicates that dry alcoholics with high SGOT levels obtain higher blood alcohol levels than those with low SGOT levels on the same dose of ethanol. This difference was not found on Day 2, after prior drinking.
Table 1. Means, Standard Deviations and t-Values for Amount of Ethanol Consumed, Dose and Peak Blood Alcohol Levels for Day 1 and Day 2 Drinking in Group I (Low SGOT) and Group II (High SGOT)

<table>
<thead>
<tr>
<th>Group</th>
<th>Weight (kg.)</th>
<th>Ethanol (ml.)</th>
<th>Dose (ml./kg.)</th>
<th>Peak BAL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Day 1</td>
<td>Day 2</td>
<td>t</td>
</tr>
<tr>
<td>Group I:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>70·59</td>
<td>233·00</td>
<td>247·00</td>
<td>2·82*</td>
</tr>
<tr>
<td>SD</td>
<td>6·32</td>
<td>29·27</td>
<td>20·84</td>
<td></td>
</tr>
<tr>
<td>Group II:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>82·45</td>
<td>240·50</td>
<td>261·50</td>
<td>1·95</td>
</tr>
<tr>
<td>SD</td>
<td>19·21</td>
<td>28·43</td>
<td>27·69</td>
<td></td>
</tr>
<tr>
<td>Group I vs II:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t</td>
<td>1·85</td>
<td>1·36</td>
<td>1·32</td>
<td></td>
</tr>
</tbody>
</table>

* p < 0·05. † p < 0·01.
Significant changes were found in blood alcohol variables for Group I but not for Group II between the first and second drinking days. Group I consumed more ethanol \( (t = 2.82, p < 0.05) \) which resulted in a larger dose \( (t = 2.70, p < 0.05) \) and achieved a higher peak blood alcohol level \( (t = 2.97, p < 0.05) \) on Day 2 as compared to Day 1.

**Fig. 1.** Mean amount of ethanol consumed each hour (bottom) and the resulting blood alcohol levels (top) for Day 1 and Day 2.

**Circadian Variation of Ethanol Metabolism.** The mean amount of ethanol consumed each hour and the resulting group blood alcohol levels for both days are illustrated in Figure 1. Blood alcohol levels increased rapidly from 1.00 to 5.00 p.m. and then increased more slowly from 6.00 to 9.00 p.m. The mean amount of ethanol consumed per hour decreased continually from 1.00 to 9.00 p.m. The increase in blood alcohol level from hour to hour was also greater in the afternoon than in the evening, suggesting that the rate of ethanol metabolism was slower in the afternoon than in the evening. However, since less ethanol was consumed in the evening than in the afternoon, it may have been that the slow increase in blood alcohol levels in the evening was a result of lower ethanol consumption. Blood alcohol levels plotted against milliliters of ethanol consumed for all subjects indicated that the rate of increase of blood alcohol level per milliliter of ethanol was much faster in the afternoon than in the evening for both days. Results of the \( 2 \times 2 \times 2 \) analysis of variance revealed no significant difference between the two SGOT groups \( (F = 0.02, NS) \). A significant effect of time of day was found with higher values (slower
rate of metabolism) for the afternoon than for the evening testing time ($F = 83.45$, $p < 0.01$). Although the main effect for days was not significant ($F = 2.38$, NS), a significant Days × Time of Day interaction was found ($F = 6.37$, $p < 0.05$). The rate of metabolism was faster in the evening than in the afternoon for both days, but metabolism was significantly faster during the afternoon of Day 2 (prior drinking) than Day 1 (prior dry). However, there was no significant difference in evening metabolism rates between Day 1 and Day 2. This interaction is illustrated in Figure 2 and indicates that prior drinking significantly increased the rate of ethanol metabolism in the afternoon but not in the evening. The interactions of SGOT levels with Days ($F = 0.25$, NS), Time of Day ($F = 0.02$, NS) and the triple interaction SGOT × Days × Time of Day ($F = 2.26$, NS) were all nonsignificant.

![Graph](image)

**FIG. 2.** Mean blood alcohol level (per cent) increase per milliliter of ethanol for the afternoon and evening of Day 1 and Day 2. High value reflects slow ethanol metabolism.

**Discussion**

These results indicate that alcoholics demonstrate a circadian variation in the rate of ethanol metabolism. Alcoholics were found to metabolize ethanol faster in the evening than in the afternoon, a finding opposite to that reported for non-alcoholics (Wilson et al., 1956; Jones, 1973b). Ethanol was also metabolized faster on the second drinking day, supporting other reports that prior ethanol intake may result in faster ethanol metabolism (Ugarte et al., 1973). However, faster ethanol metabolism was
only found during the afternoon of the second drinking day, indicating that metabolism in the evening was not affected by one day's previous drinking. SGOT levels were not related to rate of ethanol metabolism in this study. Patients with low SGOT levels (more normal liver function) drank significantly more ethanol and achieved higher peak blood alcohol levels on Day 2 than on Day 1, while this difference was not found in the high SGOT group. This may imply that the residual effect of drinking is greater for alcoholics with high SGOT levels. Although SGOT values were not measured following alcohol ingestion, it may be that alcoholics with low SGOT values increased SGOT activity as reported by Bang et al. (1958) while those with high SGOT values showed no change as reported by Mendelson et al. (1966).

The finding of circadian variations in ethanol metabolism in alcoholics may also help explain the inconsistent findings between alcoholics and non-alcoholics in rate of ethanol metabolism (Wallgren and Barry, 1970). Alcoholics may have an overall faster rate of ethanol metabolism than non-alcoholics, but if the two groups are compared in the afternoon, the slow metabolic rate of the alcoholic may be similar to the fast metabolic rate of the non-alcoholic and significant differences may not be found. If the groups are compared in the evening, then the fast metabolism of the alcoholic should be evident as compared to the slow metabolism of the non-alcoholic.

In order to verify that a complete circadian variation exists in the rate of ethanol metabolism in alcoholics, it would be necessary to monitor metabolic rates during a 24-hour period. This becomes complicated because of the difficulty in administering alcohol and measuring blood alcohol levels during the sleep cycle. However, it would be possible to assess ethanol metabolism during the morning hours without much difficulty.

It is possible that the difference in metabolic rate in the present study was not entirely a result of time of day. The slow increase in blood alcohol levels in the evening may have been related to the existing blood alcohol level. That is, a negative feedback system may exist so that after a certain blood level is reached that ethanol is metabolized more rapidly in order to prevent a toxic condition from developing. Therefore, the first part of the study should be repeated beginning at 6.00 p.m. to determine the rate of increase of blood alcohol levels from a zero level.

These results do indicate that if an alcoholic begins to drink in the afternoon and continues drinking into the evening, that he will metabolize the ethanol faster at night. Thus, he can drink a large amount in the evening without obtaining a much higher blood alcohol level. This finding is consistent with other reports that relatively large amounts of ethanol are required by alcoholics during the late afternoon and evening to maintain established blood alcohol levels (Mello and Mendelson, 1971). When the alcoholic begins to drink again the next day, he may metabolize the ethanol quicker than the previous afternoon and consequently will drink more ethanol. This may account for the large amounts of ethanol that alcoholics are capable of consuming. If the circadian variation of ethanol metabolism in alcoholics is different from non-alcoholics, then other circadian rhythms may also be different. Whether an individual has altered circadian rhythms prior to becoming an alcoholic or whether the chronic ingestion of ethanol alters these
rhythms needs to be investigated. If circadian rhythms other than the rate of ethanol metabolism are different for dry alcoholics than for non-alcoholics, then it may be difficult for the alcoholic to adjust to normal living conditions. If drying out the alcoholic does not reinstate the normal circadian rhythms, then it may be necessary to manipulate the various rhythms by such techniques as biofeedback in order to reinstate the alcoholic’s biological rhythms so that they are in phase with his social environment.

References


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