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Circadian variation of the acute and delayed response to alcohol: investigation of core body temperature variations in humans

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Abstract

Very little research has been conducted on the interaction between alcohol and circadian rhythms, particularly using human subjects. This study focuses on humans' acute and delayed response to alcohol intoxication at different times of the day.

The study, conducted over 8 weeks, was a within-subjects design with social drinkers consuming a dose of alcohol that would achieve a blood alcohol concentration (BAC) of 0.10 g/100 ml at either 1300 or 1800 h (or no beverage). Relative to the no-alcohol condition, the acute effect of drinking alcohol at 1300 h was a decrease in subjects' core body temperature, however, a similar effect was not evident after drinking alcohol at 1800 h. Moreover, irrespective of time of ingestion, alcohol consumption had an effect on core body temperature between 2330 and 0830 h. This delayed effect was ascribed to as a dampening of the core body temperature trough due to alcohol compared to the no-alcohol condition.

Keywords: Body temperature; Alcohol; Circadian rhythm; Hangover; Chronopharmacology; Sleep

1. Introduction

Chronopharmacological researchers have demonstrated the importance of biological rhythms to the appearance and severity of symptoms and medication effectiveness for many diseases. Accordingly, if biological timing influences an individual's response to medication, it is plausible that the pharmacokinetics and response to recreational drugs such as alcohol would also be dependent on administration time. Research has shown that circadian rhythms can influence the response to alcohol in humans. Alcohol has been shown to produce greater impairment on reports of subjective states or performance tasks, when it was consumed during the early activity phase (Horne and Baumer, 1991; Horne and Gibbons, 1991; Jones, 1974; Lawrence et al., 1983; but cf. Yap et al., 1993; Reinberg, 1992).

Similarly, temporal changes in the pharmacokinetics of alcohol have also been reported. For example, Lakatua et al. (1984) demonstrated that absorption was faster after alcohol ingestion at 1000 h compared with 2200 h in human subjects. Further, circadian variations in the elimination of alcohol have also been found. A study by Sturtevant et al. (1978) found minimal elimination of alcohol occurred between 1200 and 2000 h while other studies also found time of day differences for peak blood alcohol concentration (BAC) (Lenné et al., 1999; Yap et al., 1993).

Most studies exploring the circadian variation of the response to alcohol in humans have examined performance, which is a highly variable measure. In contrast, a great deal of the research on the effect of biological timing of alcohol has been undertaken using the stable physiological measure of core body temperature of rats as a dependent variable. Significantly increased hypothermia has been found in rats when they were injected with alcohol during the dark phase in comparison to the light phase (Baird et al., 1998; Brick et al., 1984; Williams et al., 1993).

To date there is very little research on the acute effects of alcohol on the body temperature of human subjects after alcohol ingestion at variable times of the day. A couple of studies with differing methodologies have been undertaken, resulting in contrasting findings (O'Boyle, 1994; Yap et al., 1993). O'Boyle found that alcohol caused a significant

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decline in oral temperature at 0800 h; in contrast, alcohol had no effect on temperature at 1600 h. In the study conducted by Yap et al. (1993), no significant time of day variations were found for the effects of alcohol on oral temperature.

Research on the effect of alcohol on body temperature during the sleep phase, using human subjects, has shown that alcohol consumption prior to sleep significantly increases core body temperature, relative to baseline levels (Danel et al., 2001; Eastman and Stewart, 1994; Mullin et al., 1933). In their study of three human subjects who consumed alcohol before sleep, Mullin et al. (1933) found that rectal temperature dropped to a lower temperature than control during the first 3 h then increased steadily for the last 5 h of sleep intersecting with control temperature and then remaining elevated above the mean control temperature for the final 4.5 hours. Following the report of Mullin et al. (1933), there have been very few controlled investigations on the effect of alcohol on temperature during the sleep phase, despite other human studies of the time-dependent effects of alcohol (Reinberg, 1992; Yap et al., 1993). Eastman and Stewart (1994) investigated whether the results reported by Mullin et al. would generalize to women and other subjects. Three subjects, two females and one male, recorded their rectal temperature while carrying out their normal activities. On three nights the subjects drank alcohol (2–6 h prior to sleep) and on other evenings (4–6 nights/subject) no alcohol was consumed. The type and amount of alcoholic beverage taken varied between and within subjects. In all three subjects, temperature was higher after alcohol consumption throughout the sleep phase. Although in Subject 3, alcohol consumption resulted in a consistent decline in temperature prior to sleep onset and then showed an increase in temperature during sleep. More recently, Danel et al. (2001) found that the core body temperature of subjects who had consumed alcohol was significantly higher at night. They used a repeated dosing method to maintain BACs at approximately 0.05 g/100 ml throughout the session. Masking effects were controlled such as lighting, subjects' activity, ambient temperature, and standardisation of meals. The mean lowest temperature was 0.36 °C higher in the alcohol session compared with the control session with seven of the nine subjects showing a hyperthermic effect of alcohol at night.

Similar findings of this rebound episode has been observed in animals (Baird et al., 1998; Gallaher and Egner, 1987; Holloway et al., 1993). These studies have shown that when rectal temperature, following alcohol injection, is collected over an extended period of time, hyperthermic disturbances are evident after the elimination of alcohol (Gallaher and Egner, 1987).

In order to extend the data of circadian variations in the response to alcohol in human subjects, and to establish whether variations due to time of alcohol ingestion are related to circadian rhythms, it is important to include circadian markers such as body temperature. The aim of this study was to investigate change across an extended period of time on core body temperature, as a function of alcohol administration time.

2. Design

A within-subjects design was used to study the effects of alcohol on core body temperature in human subjects. A no-alcohol control condition was included in this study to establish baseline data. This was a no-beverage condition used to explore the normal circadian pattern of core body temperature. The subjects were informed when they would be undertaking an alcohol condition (part of the ethical guidelines of this study). They were told that they would receive a high dose of alcohol, however, they were not informed of the exact dose they would receive. The target BAC for the alcohol condition was 0.10 g/100 ml. The alcohol administration times were 1300 and 1800 h. These times were selected based on their social applicability and more so these times are the most commonly used in the research literature on the chronopharmacology of alcohol, thus enabling comparison of findings. The alcohol and time of day conditions were counterbalanced for all subjects, noting that there was at least 1 week between each testing session for each subject.

2.1. Subjects

Twelve individuals (four males and eight females), identified as moderate drinkers (drinking on average, 2 days/week, S.D. = 1) having an average of 4.3 standard drinks on these occasions (S.D. = 2.3), were recruited from the student population of James Cook University. They were aged between 18 and 40 years (M = 25.1, S.D. = 6.9), their weights ranged between 52 and 80.5 kg (M = 69.7 and S.D. = 10.7), and their heights ranged between 163 and 182 cm (M = 170.1 and S.D. = 7.4).

To be eligible for the study, subjects were required to be free from drugs (including tobacco) or prescribed medication, and have not used recreational drugs more than once/month, not have a history of excessive or low alcohol use, and not receiving counselling/medical treatment. All subjects reported drinking only at night. It was a requirement of this study that subjects were 'Neither' chronobiological type, that is, neither a "Morning" or an "Evening" chronobiological type (Lehtonen and Graham, 1998) (M = 111.7, S.D. = 12.6). James Cook University Human Ethics Committee approved the current study (Ethics approval H927) and the subjects gave written informed consent.

Prior to experimental sessions, control over the food and fluid intake of subjects was facilitated by the provision of a snack.[1] This food was eaten 3 h prior to the alcohol

[1] The snack consisted of a small muesli bar and a snack size container of preserved fruit.

administration time. No food or drinks (except water) were consumed after this time. Subjects abstained from alcohol for 24 h prior to the experimental sessions.

2.2. Materials

2.2.1. Breathalyser

BAC was estimated from breath alcohol concentration (BrAC) using a Dräger Alcotest 7410^{Plus}Breathalyser, manufactured by Dräger Australia. The measurement range of this breathalyser was 0.00% to 0.300%. The measurement accuracy of readings from 0 to 0.1% was $\pm$0.0005%. For readings greater than 0.1%, the accuracy was $\pm$5% of the measured value. The breathalyser was recalibrated according to technical instructions (every 6 months).

2.2.2. Alcohol

Alcohol was administered in the form of Smirnoff Vodka 37.5% alc/vol. The dose of alcohol was calculated per litre of body water (Watson et al., 1981) and chosen to achieve a peak BAC of 0.10 g/100 ml.

2.2.3. Core body temperature

Core body temperature was measured at 1-min intervals using portable T-Tec electronic data loggers (Temperature Technology, Henley Beach, Australia). The subject inserted a disposable rectal probe, and attached the other end of the probe into the data logger. The temperature data recorded were downloaded onto a windows platform computer by connecting the electronic data logger to the computer.

2.3. Procedure

Subjects were required to arrive 1 h prior to the testing time of day (1300 or 1800 h). Subjects began logging their rectal temperature. Breath readings were taken every 15 min (30 min after the alcohol dose was ingested). This gave a total of 14 readings/alcohol session. Rectal temperature was recorded for 16 h (1700–0900 h) for the evening condition and 21 h for the afternoon condition (1200–0900 h). This recording time was chosen to acquire data during the sleep phase after drinking and the beginning of the light phase. Subjects were given the allocated dose of alcohol in cups to be drunk over 30 min. Subjects did not observe preparation of the beverages. Subjects were in the laboratory for the first 6 h of the total sampling time. The ambient temperature in the laboratory during the experimental sessions (6 h) was 23 °C with a variation of 1 °C, although the ambient temperature could not be controlled once subjects left the laboratory setting. Light intensity was controlled throughout for both time of day conditions to eliminate any effects on temperature due to light. Thus, for both afternoon and evening experimental sessions, the lighting environment was constant (250–500 lx: that of normal room lighting). To elucidate any further variations in response to alcohol, following alcohol consumption, biochemical, performance, and subjective state data were collected from subjects (these data are presented in this paper). When subjects were not undergoing experimental procedures, they were required to relax in a designated waiting room. Upon leaving the laboratory, subjects were told to stay at home, relax, and go to bed as normal. They removed the probe at 0900 h, before food, the following morning. Seven of the 12 subjects reported going to sleep between 2330 and 0130 h and waking between 0700 and 0900 h. The other five subjects did not report their sleep and wake times. Debriefing was undertaken at the end of the four sessions and subjects were paid AUS$100 for their time and involvement in the study.

2.4. Data analysis

Core body temperature data were inspected visually for missing values and replaced by a linear interpolation procedure. Periods of missing data were no longer than 5 min for any one condition. The BrAC and rectal temperature data were analysed using planned orthogonal polynomial contrasts and trend analysis. An alpha level of .05 was used for all statistical analyses.

3. Results

3.1. Chronokinetics of alcohol

Fig. 1 displays the mean BrAC data. There was no significant time of day difference in BrAC between the 1300 and 1800 h conditions [$F(1,11)=0.034$, $P=.86$]. As

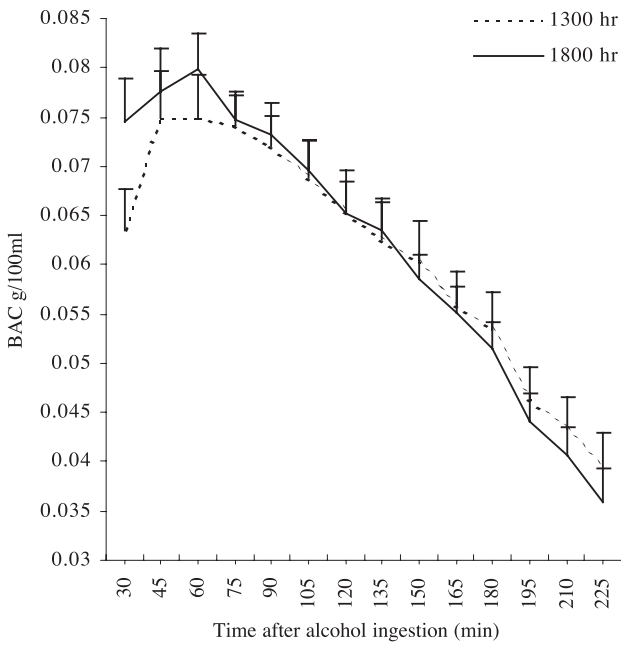

Fig. 1. Mean BAC curves for afternoon and evening alcohol sessions across the testing session. Vertical bars depict standard error of means.

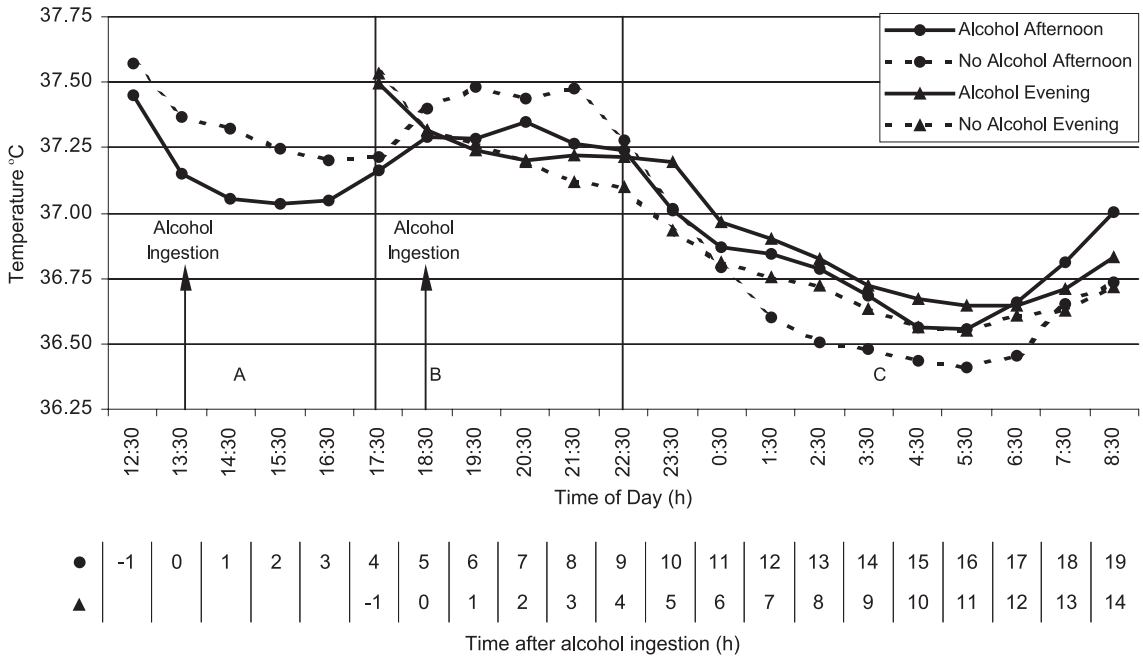

Fig. 2. Core body temperature (°C) for the four conditions for the total logging time.

would be expected for a BrAC curve, there were significant trends across time. Planned contrasts indicated that the linear [$F(1,11)=227.24$, $P<.01$], quadratic [$F(1,11)=32.88$, $P<.01$], and cubic [$F(1,11)=23.47$, $P<.01$] trends were significant. Moreover, as expected for a BrAC curve, there was an initial step increase in BrAC levels, followed by a brief plateau, and then a decline. The interaction between time of day and time postalcohol ingestion was also significant [$F(1,11)=6.65$, $P=.03$]. This interaction was linear, illustrating that while the decline is similar for both curves, prior to 75 min postingestion, the 1800 h condition had a higher initial BrAC reading and appeared to obtain a higher peak. However, paired t tests between afternoon and evening on the first four points revealed no significant differences in BrAC between the two times of the day (all P values >.06).

3.2. Core body temperature

Fig. 2 shows the mean core body temperature for the four experimental conditions and respective solar time. The data have been averaged into 1-h blocks (1-min sampling bins). For the first six points of each temperature curve, the subjects were in the laboratory for experimentation, which enabled control over activity and ambient temperature. After this time (5–14 h), subjects were in their homes. These data were analysed separately.

Table 1
Time after alcohol ingestion (acute) and relative solar times for the afternoon and evening alcohol conditions

Time postalcohol ingestion (h)	Afternoon	Evening
−1	1200–1300 h	1700–1800 h
0	1300–1400 h	1800–1900 h
1	1400–1500 h	1900–2000 h
2	1500–1600 h	2000–2100 h
3	1600–1700 h	2100–2200 h
4	1700–1800 h	2200–2300 h

3.3. Acute effects

Time after alcohol ingestion was determined from the completion of drinking (1330 or 1830 h) to the midpoint of a block of rectal temperature data. For example, 2-h post alcohol ingestion was calculated as 1330 to 1530 h. The corresponding solar time for time after alcohol ingestion for the time of day conditions is presented in Table 1.

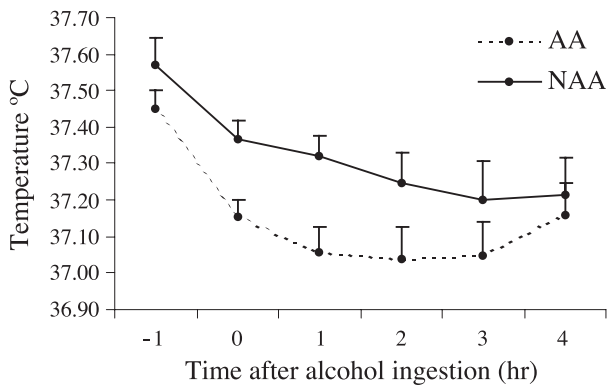

Fig. 3. Change in core body temperature (°C) across time for the alcohol and control conditions in the afternoon. Vertical bars depict standard error of means.

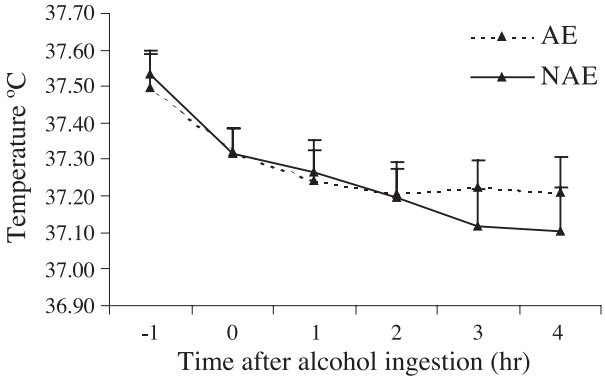

Fig. 4. Change in core body temperature (°C) across time for the alcohol and control conditions in the evening. Vertical bars depict standard error of means.

To investigate whether core body temperature was equivalent prior to alcohol consumption, a 2 (alcohol) × 2 (time of day) ANOVA was conducted on the data at −1. The main effects and interaction were not statistically significant (all *P* values >.3). This indicated that there were no significant differences between conditions at this point.

The data from each time of day were analysed using planned contrasts and trend analysis. The results of two subjects were excluded from the analysis due to an incorrect logging procedure resulting in loss of a large amount of data. There was no significant effect of time of day [$F(1,9)=0.61$, $P=.46$], or alcohol [$F(1,9)=2.00$, $P=.19$]. As would be expected, there was a significant change in body temperature across time, for both linear and quadratic trends, respectively [$F(1,9)=24.24$, $P<.01$; $F(1,9)=125.58$, $P<0.01$]. The analysis was separated out into the two times of day to determine the effect of alcohol at each time of day condition (see Figs. 3 and 4).

In the afternoon, the body temperature of subjects under the alcohol condition was clearly lower than under the control condition [$F(1,9)=6.39$, $P=.03$]. There were significant trends across time postingestion, linear and quadratic [$F(1,9)=27.58$, $P<.01$; $F(1,9)=48.88$, $P<.01$]. The interaction between alcohol condition and time was not significant [$F(5,45)=1.10$, $P=.36$]. In contrast to the afternoon temperature analysis, there was no significant alcohol effect on temperature in the evening condition [$F(1,9)=0.13$, $P=.73$]. However, there were similar trends in body temperature across time (linear and quadratic) [$F(1,9)=10.50$, $P=.01$; $F(1,9)=14.18$, $P<.01$]. Like the afternoon condition, the interaction between alcohol condition and time was not significant [$F(5,45)=1.19$, $P=.33$]. The linear trends were due to the decline in body temperature from −1 to 0 as removal of the first hour of body temperature removed the significant linear trend. The increased body temperature for the first hour of measurement was most likely the result of insertion, and adjustment to, the rectal probe.

3.4. Delayed effects

The results from the logging of core body temperature 5–14 h postingestion of alcohol are illustrated in Fig. 5. Table 2 shows the corresponding solar times. There was a significant effect of time of day [$F(1,9)=34.21$, $P<.01$]. As expected, body temperature in the afternoon condition was higher than body temperature in the evening condition. However, there was no significant effect of alcohol after ingestion at these two times of the day [$F(1,9)=0.76$, $P=.41$]. There were significant linear and cubic trends across time [$F(1,9)=72.46$, $P<.01$; $F(1,9)=8.15$, $P=.02$]. There was no significant interaction between time of day and alcohol condition [$F(1,9)=.44$, $P=.52$], nor were there any alcohol condition and hours postingestion linear or quadratic trends (all *P* values >.10). The interaction between time of day and hours postalcohol ingestion was significant showing linear, quadratic, and cubic interaction trends, respectively [$F(1,9)=13.24$, $P<.01$; $F(1,9)=33.94$, $P=.01$; $F(1,9)=5.12$, $P=.05$]. In the afternoon, body temperature was stable from 5 to 10 h postingestion time and steadily declined until 14 h post-

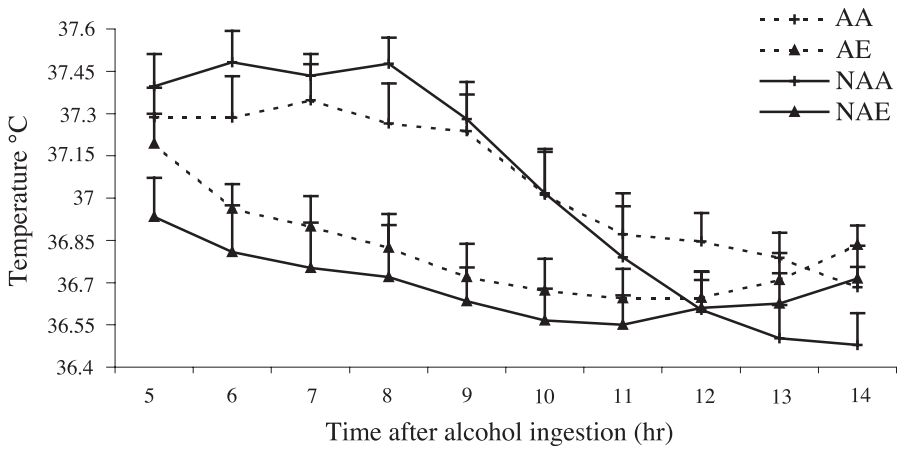

Fig. 5. Mean core body temperature for the four conditions across time (5–14 h). Vertical bars depict standard error of means.

Table 2
Time after alcohol ingestion (delayed) and relative solar times for the afternoon and evening alcohol conditions

Time postalcohol ingestion (h)	Afternoon	Evening
5	1800–1900 h	2300–2400 h
6	1900–2000 h	2400–0100 h
7	2000–2100 h	0100–0200 h
8	2100–2200 h	0200–0300 h
9	2200–2300 h	0300–0400 h
10	2300–2400 h	0400–0500 h
11	2400–0100 h	0500–0600 h
12	0100–0200 h	0600–0700 h
13	0200–0300 h	0700–0800 h
14	0300–0400 h	0800–0900 h

ingestion time. Under the evening conditions, body temperature declined from 5 to 10 h postingestion time and began to increase up until 14 h postingestion time. Contrasts restricted to temperature data collected in the afternoon conditions showed a significant linear alcohol condition by hours after alcohol ingestion interaction [$F(1,9) = 8.48$, $P = .02$]. Under the no-alcohol condition, body temperature declined across time, while under the alcohol condition, body temperature also declined but not to the same extent as the control condition.

To determine whether previous alcohol ingestion affected core body temperature across the sleep phase, analyses were conducted on the data from the solar time of 2330 to 0830 h (see Fig. 6). A statistically significant effect of alcohol on core body temperature was noted [$F(1,9) = 6.46$, $P = .03$]. It was found that previous ingestion of alcohol significantly increased core body temperature across the sleep phase regardless of the time of day it was ingested (Fig. 2). While the effect of time of day was not significant [$F(1,9) = 1.61$, $P = .24$], the effect of time was significant, showing linear and quadratic trends in body temperature change across time [$F(1,9) = 7.13$, $P = .03$; $F(1,9) = 31.27$, $P < .01$, respectively]. None of the interactions were statistically significant.

4. Discussion

This study focused on the effect of alcohol administration time on the pharmacokinetics of alcohol and its effect on core body temperature. The body temperature of subjects who had consumed alcohol declined, although only when subjects consumed alcohol in the afternoon condition (see Fig. 3). While the alcohol administration times of the current study differ to a number of the previous studies addressing the chronopharmacology of alcohol, the current study showed support for the contention that alcohol has a greater effect when it was consumed earlier in the day, 1300 h compared with 1800 h.

Studies in animals purport that the largest decreases in body temperature are found when animals are injected with alcohol during the dark phase (activity phase) of their diurnal cycle (Baird et al., 1998; Brick et al., 1984). Additionally, O'Boyle found that alcohol caused a significant decline in oral temperature at 0800 h; in contrast, alcohol had no effect on temperature at 1600 h.

It could be contended that the difference between the alcohol and no-alcohol afternoon conditions may possibly be due to sampling error that might not have been detected because the data were averaged over a 1-h time period. This contention was addressed by examining whether the difference between the two conditions (± 0.071) for the baseline period (1200–1259 h) at 1-min intervals was significant. A t test revealed a significant difference between the two groups at baseline. As such, subsequent analysis of the temperature data (at 1-min intervals) for the acute period (4 h) was undertaken controlling for the baseline variation. It was found that the difference between the alcohol and no-alcohol conditions remained statistically significant. Thus, it is forwarded that the difference between the alcohol and no-alcohol conditions (postalcohol consumption) is most likely due to alcohol ingestion and not sampling error.

Analysis of the delayed effects of alcohol showed that alcohol, statistically, had significant effects on core body

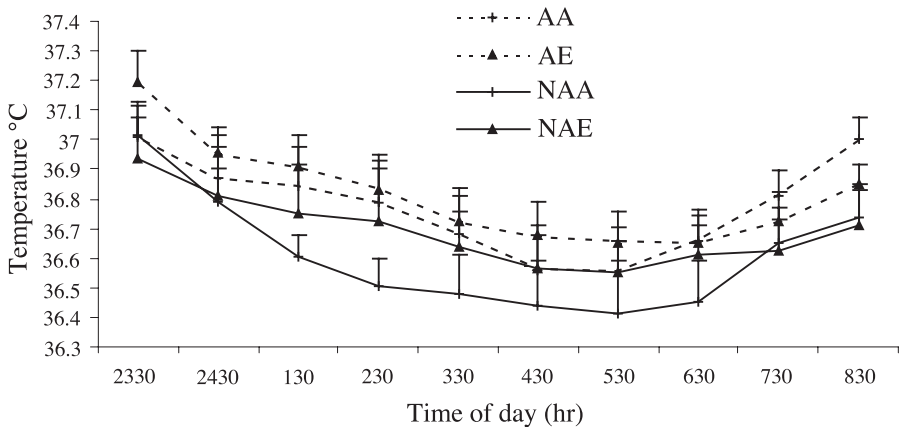

Fig. 6. Mean core body temperature across the sleep phase for the four conditions with corresponding standard error.

temperature up to 14 h postalcohol ingestion. Ingestion of alcohol at 1300 h lowered subjects' body temperature compared to the no-alcohol condition from 5 to 9 h after alcohol consumption corresponding to a solar time of (1830–2230 h). After this time, the body temperature of subjects who had not drunk alcohol began to decline while the body temperature of subjects who had consumed alcohol did not decline to the same extent. In the evening condition, alcohol had the effect of elevating body temperature compared to the no-alcohol condition; although conditions showed similar trends across time. The delayed body temperature data were consistent with the results of other researchers who have observed the rebound episode in animals (Baird et al., 1998; Gallaher and Egner, 1987; Holloway et al., 1993) and the effect of alcohol on body temperature during the sleep phase, using human subjects (Danel et al., 2001; Eastman and Stewart, 1994; Mullin et al., 1933). While it could be contended that these findings could be due to homeostatic mechanisms, the fact that the increased body temperature values occurred throughout the sleep phase, regardless of time of alcohol ingestion (1300 or 1800 h), may be suggestive of a circadian disruption. Subjects who consumed alcohol did not experience the normal circadian core body temperature decline throughout the sleep phase. Despite the fact that the design and procedures used in these studies (Danel et al., 2001; Eastman and Stewart, 1994; Mullin et al., 1933) differed considerably, for example, doses of alcohol, control over subjects' sleep/wake and activity levels, and food intake, consistently, it has been shown that alcohol consumption has an impact on body temperature during the sleep phase. The current study did not use a constant routine; as such masking effects such as ambient temperature, activity, food intake, were not completely controlled. Therefore, it is possible that these extraneous variables could have influenced the results of this study. While the studies by Mullin et al. (1933), and Eastman and Stewart (1994) did not control for masking effects, the study by Danel et al. (2001) did utilise a tightly controlled procedure. Regardless of experimental design and procedural differences, all of these studies consistently demonstrate the same trend; alcohol ingestion increases body temperature during the sleep phase relative to a no-alcohol ingestion condition, supporting the data of the present study.

In summary, this study adds to the current literature on the interaction between alcohol and circadian rhythms using human subjects. At present, very little research on the effect of alcohol on human core body temperature has been undertaken. It is important that future research should be directed towards investigation of the interaction between alcohol and the biological rhythm, that is, collection of data (e.g. core body temperature and melatonin) over a number of cycles. Additionally, this study highlights the need for future research to include more alcohol administration times, for example, a very early morning time and a very late evening time in order to obtain a clearer picture of the chronopharmacology of alcohol.

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