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Urine methanol concentration and alcohol hangover severity

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ABSTRACT

Background: Congeners are substances, other than ethanol, that are produced during fermentation. Previous research found that the consumption of congener-rich drinks contributes to the severity of alcohol hangover. Methanol is such a congener that has been related to alcohol hangover. Therefore, the aim of this study was to examine the relationship between urine methanol concentration and alcohol hangover severity.

Methods: N = 36 healthy social drinkers (22 females, 14 males), aged 18–30 years old, participated in a naturalistic study, comprising a hangover day and a control day (no alcohol consumed the previous day). N = 18 of them had regular hangovers (the hangover group), while the other N = 18 claimed to be hangover-immune (hangover-immune group). Overall hangover severity was assessed, and that of 23 individual hangover symptoms. Urine methanol concentrations on the hangover and control days were compared, and correlated to hangover (symptom) severity.

Results: Urine methanol concentration was significantly higher on hangover days compared to control days ($p = 0.0001$). No significant differences in urine methanol concentration were found between the hangover group and hangover-immune group. However, urine methanol concentration did not significantly correlate with overall hangover severity ($r = -0.011$, $p = 0.948$), nor with any of the individual hangover symptoms. These findings were observed also when analyzing the data separately for the hangover-immune group. In the hangover group, a significant correlation with urine methanol concentration was found only with vomiting ($r = 0.489$, $p = 0.037$).

Conclusion: No significant correlation was observed between urine methanol concentration and hangover severity, nor with individual core hangover symptoms.

1. Introduction

The alcohol hangover refers to the combined variety of symptoms experienced the day after an evening of heavy alcohol consumption (Penning, McKinney, & Verster, 2012), including being tiredness, thirst, drowsiness, sleepiness, headache, dry mouth, nausea, weakness, concentration problems, and reduced alertness. Despite the long history of alcohol consumption, and the negative effects of having a hangover on mood (McKinney, 2010) and performance of daily activities such as driving a car (Verster et al., 2014), little is known about the pathology underlying the alcohol hangover (Penning, van Nuland, Fliervoet, Olivier, & Verster, 2010) and no effective treatments are currently available (Pittler, Verster, & Ernst, 2005; Verster & Penning, 2010).

In addition to the amount of alcohol consumed, several other factors have been proposed that may explain intra- and inter-individual differences in the presence and severity of hangover symptoms (Verster et al., 2010). Among these are activities during the evening of alcohol consumption (e.g., dancing or sitting at a bar) (Prat, Adan, & Sanchez-Tuert, 2009), peak BAC that was reached (Penning et al., 2010), total sleep time (Rohsenow et al., 2010), and which types of alcoholic beverages were consumed (Verster, 2008). Regarding different types of alcoholic beverages, it has been reported that, with the same amount of alcohol consumed, hangovers

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are usually worse after consuming spirits when compared to wine or beer (Verster, 2008). An explanation for this may be found in the variation of the presence or absence of so-called congeners. Congeners are compounds that occur naturally in alcoholic beverages because of distilling and fermenting processes (Rohsenow et al., 2010). Often these are other alcohols than ethanol, or their metabolites (Jones, 1987). Congeners may contribute to the flavor, bouquet, and color of alcoholic drinks. The notion that congener content differs between distilled spirits and other alcoholic beverages is not new. For example, already in 1957, Snell showed that although the ethanol content of whiskeys ranged from 40% and 50%, the variation in congener content of these beverages was much greater (Snell, 1958). Other early studies revealed that consumers reported less hangover after drinking vodka when compared to the same amount of whisky (Damrau & Liddy, 1959, 1960). Additionally, it was also found that hangover severity scores were significantly higher after consuming bourbon when compared to vodka (reaching a peak BAC of 0.11%.) However, the difference in congener content had no impact on performance impairment seen on a series of neuropsychological tests (Rohsenow et al., 2010).

Although many congeners have been identified, methanol is considered to be one of the congeners that may significantly contribute to the development of alcohol hangover (Bendtsen, Jones, & Helander, 1998; Jones, 1987). Methanol is a product of sugar fermentation. Concentrations of methanol differ significantly among alcoholic beverages, and were found to be highest in red wine and in distilled spirits such as brandy and whiskeys, whereas methanol concentrations were lowest in beer and vodka (Bonte, 1987). Alcoholic beverages containing more methanol are associated with a higher incidence and severity of hangover than are beverages containing relatively less methanol (Jones, 1987). Methanol elimination from the body coincides with alcohol hangover onset (Jones, 1987; Ylikahri, Huttumen, Eriksson, & Nikkila, 1974). Methanol's metabolites, formaldehyde and formic acid, are highly toxic to the human body, and thus may contribute to hangover symptoms (Jones, 1987). Both methanol and ethanol are substrates for hepatic alcohol dehydrogenase (ADH). However, the affinity of the enzyme is much higher for ethanol than it is for methanol (Mani, Pietruszko, & Theorell, 1970). Consequently, biotransformation of methanol is blocked when ethanol fully occupies ADH. Thus, methanol concentrations linger until the levels of ethanol drop (Majchrowicz & Mendelson, 1971). In other words, if ethanol is still found in urine, it can be assumed that the vast majority of methanol that is present is consumed as congener, and not formed by ethanol metabolism.

To our knowledge, only one study directly examined the relationship between methanol concentration and the presence and severity of hangover symptoms. In this study, conducted in South Korea, Woo et al. measured blood methanol concentrations in 18 healthy male subjects (Woo et al., 2005). Participants consumed alcohol (Soju, 1.5 g/kg), and blood samples were collected the next day, 13 hours thereafter. Hangover severity was assessed using Ylikahri's subjective and somatic hangover scales (Ylikahri et al., 1974). When controlling for blood ethanol levels, a significant positive correlation was found between methanol concentration and the subjective hangover severity scale, but not with the somatic hangover severity scale.

Given the limited scientific information on the role of methanol as congener in the pathology of alcohol hangover, the relationship between urine methanol concentration and hangover symptom severity in social drinkers was determined.

2. Materials and methods

2.1. Participants

Participants were regular social drinkers, 18–30 years old, who reported consuming at least five alcoholic beverages per occasion, at least three times per month. Participants were required to be healthy volunteers, and not using recreational drugs. To be included, participants had to consume sufficient amounts of alcohol to produce an alcohol hangover. This was determined by asking the number of alcoholic drinks they usually consume within a certain time frame, in order to calculate their estimated peak Breath Alcohol Concentration (BAC) on such evenings. The estimated BAC was computed according to the modified Widmark formula (Watson, Watson, & Batt, 1981), taking into account drinking time and amount of alcohol consumed, and controlling for gender and body weight. Participants were included if the estimated BAC was higher than 0.08%. Two groups of participants were included: N = 18 participants who reported having hangovers and N = 18 participants who claimed to be hangover-free, although they regularly consumed alcohol to reach estimated BACs higher than 0.08%.

2.2. Study design

Subjects participated in a naturalistic study, comprising a hangover day and a control day (no alcohol consumed the previous day). Characteristic for a naturalistic study design is the fact that no constraints are posed on participants' behavior. Thus, alcohol was consumed in a setting of their own choice, and the investigators had no influence on the type and quantity of alcohol consumed. It was not mandatory to consume alcohol on scheduled test days, and these were postponed if participants chose not to do so. Participants were not allowed to consume any alcoholic beverages 24 hours prior to the alcohol-free control day. There was no influence by the investigators, as these were not present. However, participants were asked not to use recreational drugs, and to consume no caffeinated beverages on the test day. The naturalistic approach has the advantage of being highly ecologically valid when compared to controlled laboratory studies, as the data are collected from real-life drinking occasions. The University of Groningen Psychology Ethics Committee approved the study, and written informed consent was obtained from all participants. The study was financially supported by and conducted at Utrecht University.

2.3. Procedures

On both the hangover day and a control day, participants came to the Institute in the morning. A urine sample was collected to determine methanol concentration, and several subjective assessments were made. These included a questionnaire on start and stop time of alcohol consumption and the number and type of drinks consumed. These data enabled calculation of the estimated peak BAC for each participant. In addition, hangover severity was assessed.

2.4. Hangover symptom severity

A 1-item overall hangover severity score, and the severity of 23 individual hangover symptoms were rated on a 10-point scale, ranging from 0 (absent) to 10 (extreme). The 23 individual items were headache, nausea, concentration problems, regret, sleepiness,

heart beating, vomiting, tiredness, shaking, clumsiness, weakness, dizziness, apathy, sweating, stomach pain, confusion, light sensitivity, thirst, heart racing, anxiety, depression, reduced appetite, and sleep problems. The items are a combination of items from the three currently most frequently used hangover scales, the Alcohol Hangover Severity Scale (AHSS), the Hangover Symptoms Scale (HSS), and the Acute Hangover Scale (AHS) (Penning et al., 2013; Rohsenow et al., 2007; Slutske, Piasecki, & Hunt-Carter, 2003).

2.5. Urine collection, handling, and analyses

On each test day, a urine sample was collected at 9:30 AM. Any turbid urine samples were centrifuged at 3000 rpm for 15 min at room temperature. The urine was stored in three 3-mL cryovials, at a temperature of −20 °C. Urine methanol concentration was determined using headspace gas chromatography with flame ionization detection. The separation was performed on a Porapak Q-packed column. Samples containing 1-propanol as an internal standard (IS) and the headspace syringe were warmed at 80 °C for 20 min in an oven, after which the gas phase in the vial was manually injected into the column of the headspace chromatograph. The temperature of the column oven was set at 140 °C for 9 min. After the elution of the IS, the temperature was increased to 200 °C for 5 min to remove any late eluting sample compounds from the column. For each standard curve sample, peak ratio of methanol to the IS was calculated and plotted against the methanol concentration. A calibration curve to determine methanol concentrations in urine with a range of 1 ppm (LOQ) to 50 ppm was used. For validation, urine samples were spiked with methanol at 1 ppm, 5 ppm, and 50 ppm. Accuracy was determined to be 91.40%, 99.98%, 95.94% (1, 5, 50 ppm, respectively). Intra-day precision was 5.5%, 9.7%, 0.90% (1, 5, 50 ppm, respectively). Inter-day precision was determined to be 17%, 2.07%, 3.01% (1, 5, 50 ppm, respectively). Results from urine samples from participants were plotted in the calibration curve, calculating methanol concentrations using the corresponding formula.

2.6. Statistical analyses

Statistical analyses were performed with SPSS, version 23. Mean and standard deviation were computed for each variable. Urine methanol concentrations of the hangover and control day were compared using nonparametric Mann-Whitney U tests. Delta scores (hangover minus control day) were computed for each variable. Delta methanol concentration was correlated with overall hangover severity, and severity scores for the individual hangover symptoms (nonparametric, Spearman's *r*). The analyses were conducted for all participants together (N = 36), and separate for the hangover group and the hangover-immune group.

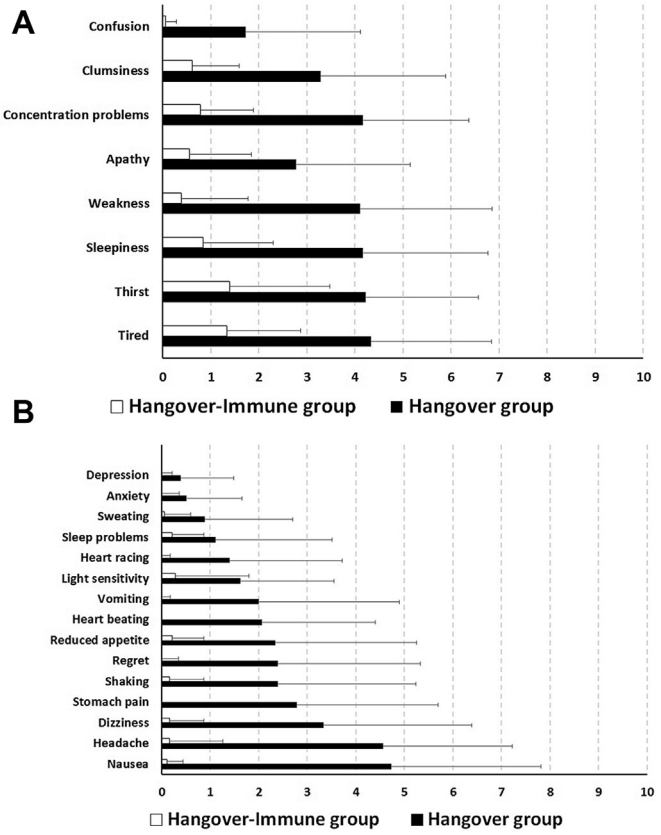

Fig. 1. Severity scores of individual hangover symptoms. Difference scores (hangover minus control day) are shown for the hangover group and hangover-immune group. Fig. 1A shows symptoms related to drowsiness, cognitive performance, and thirst; Fig. 1B shows the other hangover symptoms. Except for anxiety and depression, all differences in symptom severity between the hangover-immune group and hangover group were statistically significant ($p < 0.05$).

3. Results

An overview of demographics of the 36 participants is given in Table 1. Participants of the hangover group (N = 18) and hangover-immune group (N = 18) did not differ significantly in age, height, and weight. No significant differences between the groups were observed regarding the total number of alcoholic drinks consumed and estimated peak BAC. Overall hangover severity was significantly higher in the hangover group ($p = 0.006$). For both groups, individual hangover symptom severity is summarized in Fig. 1. It is evident from Fig. 1 that severity scores in the hangover group are significantly higher when compared to the hangover-immune

Table 1
Descriptives of the study population.

	Hangover-Immune Group	Hangover Group	All participants
	N = 18	N = 18	N = 36
Male/Female ratio	8 (44.4%)/10 (55.6%)	6 (33.3%)/12 (66.7%)	14 (38.9%)/22 (61.1%)
Age	20.8 (2.0)	21.4 (1.6)	21.1 (1.8)
Height (m)	1.79 (0.1)	1.76 (0.1)	1.77 (0.1)
Weight (kg)	71.1 (10.2)	67.2 (11.5)	69.2 (10.9)
Alcoholic drinks consumed	10.7 (4.7)	12.5 (7.3)	11.6 (6.1)
Estimated BAC (%)	0.17 (0.07)	0.19 (0.09)	0.18 (0.08)
1-item overall hangover severity	0.7 (1.4)	5.6 (2.4) *	3.1 (3.2)

Mean values are presented with standard deviation between brackets. Significant differences ($p < 0.05$) between the hangover group and hangover immune group are indicated by *.
Abbreviations: BAC = breath alcohol concentration.

group. Moreover, whereas drinkers with a hangover endorse a variety of symptoms, including those that may have a significant impact on daily activities (see Fig. 1B), in hangover-immune drinkers the hangover state seem to be limited to mild sleepiness-related symptoms (see Fig. 1A). These and other differences between the hangover and hangover-immune group are discussed in detail elsewhere (Hogewoning et al., 2016).

Overall (N = 36), urine methanol concentration ($p = 0.0001$) was significantly higher on the hangover day compared to the control day (see Table 2). For the hangover group, on the hangover day a significantly higher urine methanol concentration was found when compared to the control day. For the hangover-immune group, urine methanol concentration was also significantly higher on the hangover day when compared to the control day ($p = 0.001$). Urine methanol concentration on the hangover day did not significantly differ between the hangover group and the hangover-immune group ($p = 0.064$). No differences between the two groups were observed on the control day ($p = 0.192$).

Urine methanol concentration did not significantly correlate with overall hangover severity ($r = -0.011$, $p = 0.948$), nor with any of the individual hangover symptoms. The absence of any significant correlations was also observed when analyzing the hangover day data separately for the hangover-immune group. For the hangover group, a significant correlation was found only between urine methanol concentration and vomiting ($r = 0.489$, $p = 0.039$). There was also no significant relationship between urine methanol and number of drinks consumed, or estimated BAC.

4. Discussion

On the hangover day, urine methanol concentration was significantly higher when compared to the alcohol-free control day. The hangover group and hangover-immune group did not significantly differ in urine methanol concentration. The latter is consistent with the fact that no differences in demographics or alcohol consumption were observed between both groups (Hogewoning et al., 2016). In addition, on the control day no significant differences were found in methanol concentration between the groups.

Interestingly, methanol was also detected in small amounts in urine samples collected on the alcohol-free control day. A possible explanation for this observation may be the presence of pectins, i.e. methyl esters and galactose, in fruit and fruit juices. When ingested beverages contain pectins, methanol may be anaerobically produced in the gut by bacteria and other metabolic fermentation processes (Axelrod & Daly, 1965). Because pectins are present in fruits, nonalcoholic beverages such as fruit juices may contribute to the production of methanol (Lindinger, Taucher, Jordan, Hansel, & Vogel, 1997; Siragusa, Cerda, Baig, Burgin, & Robbins, 1988). Hence, if these beverages are consumed on the alcohol-free control day, small quantities of methanol may be detected in urine. Urine methanol concentration did not significantly correlate with overall hangover severity, nor with any of the individual hangover symptoms. A similar absence of significant correlations was observed for the hangover immune group, whereas for the hangover group only vomiting was significantly associated with urine methanol concentration.

Additional analyses revealed that urine ethanol could be demonstrated in all but one subject (Van de Loo et al., 2016). This finding supports the idea that the methanol that was detected in urine comes from the consumption of congener-rich beverages, and not from ethanol metabolism. Taken together, the data suggest that consuming methanol-rich beverages does not have a significant effect on the severity of alcohol hangover symptoms.

In 1957, Snell already suggested that research was needed to examine the potential consequences of consuming congener-content drinks for alcohol hangover, and suggested that some congeners may be more important in this regard than others (Snell, 1958). Pawan was one of the first researchers who examined the impact of congener content on the presence and severity of alcohol hangover (Pawan, 1973). In N = 20 healthy male volunteers, Pawan examined hangover severity after consumption of a variety of alcoholic beverages such as white and red wine, rum, whiskey, gin, and brandy. Results were compared to occasions on which the subjects consumed diluted ethanol (very few congeners present). Pawan showed that hangover severity was proportional to the congener content of the alcoholic drinks. In addition, hangovers were experienced most frequently on occasions when high congener-containing drinks such as brandy were consumed (Pawan, 1973). The fact that the amount of congeners widely differs between alcoholic drinks was also demonstrated by Nathan et al., who showed that bourbon contained 37 times more congeners than vodka (Nathan, Zare, Ferneau, & Lowenstein, 1970). However, the most extensive research on congener content of alcoholic drinks comes from Wolfgang Bonte, who determined the congener content of over 3000 different alcoholic drinks (Bonte, 1987). In contrast to previous research (Woo et al., 2005), and to our surprise, urine methanol content was unrelated to hangover severity. Because part of the methanol may be metabolized or excreted, future research should update the congener content listing of Bonte to enable examining whether amounts of methanol that were actually consumed by participants via various beverages is related to next-day hangover severity (Bonte, 1987).

The current findings partly contrast with those of Woo et al. (2005) who reported a significant association between methanol concentration and subjective hangover severity. However, Woo et al. also did not find a significant relationship for somatic hangover symptoms. There are several methodological differences between the study by Woo et al. and our study that may account for the observed deviation in study outcomes. First, the current study applied a naturalistic design whereas Woo et al. conducted a controlled laboratory experiment. In contrast to the current study, Woo et al. included only men, participants consumed only one type of alcoholic beverage, and all were dosed to achieve the same BAC. Woo et al. used the composite hangover severity score (Ylikahri

Table 2
Urine methanol concentration.

	Hangover-immune Group		Hangover Group	
	Urine methanol concentration control day	Urine methanol concentration hangover day	Urine methanol concentration control day	Urine methanol concentration hangover day
Mean (mg/L)	1.16	3.54	2.15	5.20
SD	0.97	2.26	2.30	2.80
Range	0.00–3.60	1.10–8.39	0.00–7.99	1.02–12.02

Mean values are presented with standard deviation between brackets. Significant differences ($p < 0.05$) between the hangover group and hangover immune group are indicated by *.

et al., 1974) which averages the severity scores of six hangover symptoms (fatigue, headache, dizziness, nausea, thirst, and tension). In contrast, in the current study a 1-item overall hangover severity score was obtained, and 23 individual symptoms were assessed. Finally, Woo et al. measured methanol concentration in blood, whereas in the current study methanol assessments were done in urine. These differences may all have contributed to the different outcomes by Woo et al. and the current study.

Several limitations regarding our study should be addressed. In general, all limitations that are common to a naturalistic study design also apply to the current investigation. That is, alcohol consumption, start and stop time of drinking, and total sleep time were not controlled by the investigators. In addition, the time between stopping drinking and urine collection varied between subjects, and the amount of water consumed during the night, if any, and possible urination was not recorded. Hence, we do not know to what extent this had an effect on urine methanol concentration. Finally, there is a possibility that the bladder already contained methanol before the alcohol consumption session.

Applying a naturalistic design also had several advantages that cannot be established in a controlled laboratory setting. As this was an observational study, the behavior of participants matches that of daily life. Most importantly, the amount of alcohol consumed by the participants would not have been approved by ethics committees to be administered in a controlled trial. While this is understandable from a safety perspective, it makes it difficult to study the alcohol hangover under controlled conditions. The fact that participants could choose their own beverages likely contributed to the inter-subject variability in the intake of methanol, allowing for correlations with the hangover symptom severity scores.

Taken together, the current data show that consumption of methanol-rich beverages does not have a major effect on hangover symptom severity. As previous research has shown that congener content does have an impact on hangover severity, future research should examine the impact of other congeners such as butanol and propanol, and the ethanol metabolite acetaldehyde.

Declaration of interest

Joris Verster has received grants/research support from the Dutch Ministry of Infrastructure and the Environment, Janssen Research and Development, Nutricia, Red Bull and Takeda, and has acted as a consultant for the Canadian Beverage Association, Centraal Bureau Drogisterijbedrijven, Coleman Frost, Danone, Deenox, Eisai, Janssen, Jazz, Purdue, Red Bull, Sanofi-Aventis, Sen-Jam Pharmaceutical, Sepracor, Takeda, Transcept, Trimbos Institute, and Vital Beverages. Karel Brookhuis has received grants/research support from NWO, the Dutch Ministry of Infrastructure and the Environment, European Commission, Wyeth, Sanofi, Schering, Nissan, JARI, Mercedes Benz, and Verbond van Verzekeraars. Johan Garssen is part-time employee of Nutricia Research. The other authors have no potential conflicts of interest to disclose.

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