Int J Legal Med (2012) 126:757–764
DOI 10.1007/s00414-012-0725-3

ORIGINAL ARTICLE

Preliminary investigations on ethyl glucuronide and ethyl sulfate cutoffs for detecting alcohol consumption on the basis of an ingestion experiment and on data from withdrawal treatment

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Received: 5 January 2012 / Accepted: 12 June 2012 / Published online: 30 June 2012

Abstract Ethyl glucuronide (EtG) and ethyl sulfate (EtS) are commonly used alcohol markers for previous alcohol consumption. Nevertheless, the optimum EtG cutoff for urinary abstinence tests is still being discussed, and no cutoff has been recommended for EtS yet. The aim of this study was to verify cutoffs by investigating EtG and EtS concentrations (c_{EtG} and c_{EtS}) in the urine of healthy persons after drinking small, but realistic amounts of alcohol (one or two glasses of beer or white wine), and to look for the window of detection in strongly alcohol-intoxicated patients who were beginning withdrawal treatment. Very high EtG and EtS concentrations were measured in the first urine samples of patients under withdrawal treatment. However, 24 h later, concentrations decreased considerably, and c_{EtG}<0.5 mg/l and c_{EtS}<0.1 mg/l were determined in 26.7 % (4/13) and 13.3 % (2/13) of the samples, respectively. Concentrations above 0.1 mg/l (EtG) and 0.05 mg/l (EtS) were measured for 23.5 and 20.5 h after consuming 0.1 l of white wine or 0.33 l of beer, and 24 h after the experiment, 75 % (9/12) of the urine samples were tested negative for EtG and EtS using the following cutoffs: EtG 0.5 mg/l and EtS 0.1 mg/l. In half of the samples, concentrations below 0.1 mg/l (EtG) and 0.05 mg/l (EtS) were detected. Urinary cutoffs for EtG of 0.5 mg/l or higher are not suitable for testing abstinence. Even 0.1 mg/l is not effective to detect the intake of small amounts of alcohol in the context of abstinence tests. For EtS, 0.05 mg/l were found to be a potential cutoff to exclude the repeated intake of alcohol. Yet, further research is required to verify this cutoff. For a limited time period, EtG and EtS concentrations within the range of these cutoffs are also detectable after unintentional consumption of alcohol. Participants of abstinence programs have to be informed about the alcohol content of certain foods and beverages whose consumption is in conflict with strict abstinence.

Keywords Ethyl glucuronide · Ethyl sulfate · Urine · Alcohol abstinence · Cutoffs

Introduction

In Germany and many other countries, ethyl glucuronide (EtG) and ethyl sulfate (EtS) are getting more and more popular as potential markers for screening previous alcohol consumption. These nonvolatile and water soluble ethanol metabolites can be detected in a variety of body fluids and tissues after alcohol consumption.

Many studies have examined EtG concentrations in serum, urine, and oral fluid after the consumption of various amounts of alcohol. Alcohol amounts, depending on the body weight of the participants (0.15–1.0 g/kg ethanol) [1–8], as well as definite amounts of alcohol (1.0–49 g

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ethanol) [9–13], were consumed in controlled drinking experiments. Further studies have monitored urinary concentrations of patients under withdrawal treatment both during detoxification and while ensuring alcohol abstinence [11, 14–17]. Based on these studies, detailed information on the kinetics of EtG and detection times in different body fluids is available. Only 0.02–0.03 % of the consumed ethanol is excreted as EtG, and 0.01–0.02 %, as EtS on a molar basis [6, 13]. Nevertheless, EtG and EtS are detectable in urine for a considerably longer period of time than ethanol itself [18]. EtG is eliminated with a half-time of ~2.5 h [2, 11, 19]. During the first 24 h following the consumption of alcohol, 95–99.5 % of the EtG/EtS are eliminated, with 79–92 % of the EtG/EtS being excreted in the first 10 to 12 h [10, 13]. Ethanol doses between ~0.25 and 0.5 g/kg are detectable for ~24–48 h after the start of ethanol ingestion [20].

In the context of abstinence tests, it is relevant to know for how long EtG concentrations in urine exceed ascertained cutoff values after drinking different amounts of alcohol. According to the current German guidelines for driving ability diagnostics, participants of controlled abstinence programs are summoned unpredictably to deliver a urine sample under visual control within the next day. In order to verify strict abstinence, it is necessary to ensure that even 24 h after the consumption of small amounts of alcohol, for example, one glass of beer or wine, EtG or EtS concentrations in urine exceed the determined cutoff values. The cutoff values, which are currently used for proving alcohol abstinence, vary from 0.1 to 1.1 mg/l [16, 21–23].

Studies showed that EtG concentrations above 0.1 mg/l can also be determined in urine after the consumption of food and beverages that contain small amounts of alcohol, such as nonalcoholic beer [24, 25] or yeast in combination with sugar [26] and after the use of alcohol-containing mouthwash [21, 27] or hand sanitizers [10, 28, 29]. Because of these results, it is essential to establish cutoff values which exclude both false positive results due to unintentional consumption of alcohol as well as negative results despite prior alcohol intake.

Many of the published studies only discuss EtG concentrations in urine. However, it was demonstrated that EtG can be formed or destroyed in urine by bacteria, especially in the case of insufficiently cooled urine samples [30–33]. Ethyl sulfate has been found to be biodegradable only under conditions of high bacterial density [34]. Consequently, EtS seems to be the more reliable marker for monitoring alcohol abstinence. However, false positive results can occur due to the consumption of EtS-containing beverages like alcohol-free wine or grape juice [22, 24]. Several studies deal with the kinetics and detection windows of EtS in urine [3, 6, 13–15, 35]. Nevertheless, there is currently no obligatory cutoff value for EtS in urine.

The present work compares different cutoff values for EtG in urine for use in abstinence programs in which the participants are given 24 h time to take the test on the basis of determined detection windows. In addition, a preliminary cutoff value for EtS in urine will be suggested.

In this context, EtG concentrations in the urine of alcohol-dependent patients, during the first days of withdrawal treatment and after a controlled ingestion experiment, were analyzed. The results of these studies are discussed and compared with data obtained from the literature.

Material and methods

Study protocol

Ingestion experiment

Twelve healthy volunteers participated in the controlled ingestion experiment. All personal data and type and quantity of the consumed drinks are summarized in Table 1. The participants fully consented to the tasks being carried out in the study and were not paid for their input. There was no relationship or dependency between the participants and the heads responsible for the study. All of them were social drinkers and had renounced alcohol-containing foods and beverages for a minimum of 80 h.

Before the start of the experiment, urine samples were collected from each participant. Within a short time period (maximum 45 min), each participant had to drink a defined small amount of alcohol as beer or wine. When selecting the amounts to be consumed (one or two glasses of white wine at 0.1 l and one or two bottles of beer at 0.33 l), emphasis was put on small amounts of alcohol that are realistically consumed in everyday life.

Urine samples were collected over 24–28.5 h. The participants were asked to deliver urine samples regularly (every 1–2 h) within the first 8 h after drinking. Urine was collected in plastic urine monovettes (Sarstedt AG & Co., Nümbrecht, Germany) without any additives and stored at −20 °C until analysis. To create a most realistic scenario, no extra instructions were given concerning the diet or smoking habits.

Patients under withdrawal treatment

Thirteen patients of the Landschaftsverband Rheinland (LVR) Klinik in Bonn, Germany, voluntarily took part in this study. All of them had arrived heavily intoxicated by alcohol with high breath alcohol concentrations at the emergency department for addictive disorders and were admitted as inpatients. Personal data of the participants and the measured breath

Table 1 Personal data of the participants of the ingestion experiment, type of drunken beverage, and consumed amounts of ethanol absolute (m_{EtOH}) as well as in relation to the body weight (m_{EtOH}/weight)

Number	Sex	Age (years)	Height (cm)	Weight (kg)	BMI (kg/cm^2)	White wine		Beer		m_{EtOH} (g)	m_{EtOH}/weight (g/kg)
						0.1 l	0.2 l	0.33 l	0.66 l		
1	Female	27	165	56	20.6	x				8.2	0.15
2	Female	36	168	68	24.1	x				8.2	0.12
3	Female	27	177	77	24.6		x			16.4	0.21
4	Female	32	168	52	18.4		x			16.4	0.32
5	Male	22	177	64	20.4		x			16.4	0.26
6	Female	31	172	55	18.6			x		11.6	0.21
7	Female	24	160	52	20.3			x		11.6	0.22
8	Female	28	168	78	27.6			x		11.6	0.15
9	Male	38	181	74	22.6				x	23.1	0.31
10	Male	26	188	80	22.6				x	23.1	0.29
11	Male	20	190	90	24.9				x	23.1	0.26
12	Male	41	182	78	23.5				x	23.1	0.30

alcohol contents are summarized in Table 2. An additional six patients discontinued participating in the study. Their data and results were deleted and not included in the evaluation.

The first urine samples were collected as soon as possible. Within the following 6 days, further urine samples were collected every 12 h. During this time period, none of the participants had access to alcohol. All participants gave informed consent, and the study protocol was approved by the Ethics Commission of the Medical Faculty of the University of Bonn.

Measurements of EtG and EtS in urine

EtG and EtS concentrations in urine were determined according to a previous published liquid chromatography-tandem mass spectrometry LC-MS/MS method [36]. Urine samples were prepared by protein precipitation. Chromatographic separation was performed on a Synergi Polar-RP column (250×2 mm, 4 μm; Phenomenex) using 0.1 % of formic acid and acetonitrile as mobile phases. Detection of the ions was performed in multiple reaction monitoring mode. The limit of detection (LOD) and limit of quantitation (LOQ) were 0.005 and 0.019 mg/l for EtG and 0.005 and 0.015 mg/l for EtS, respectively. For further details and validation data, see Albermann et al. [36].

Urine samples with EtG concentrations between 0 and 0.5 mg/l were additionally examined immunochemically, using the DRI® EtG assay on an Olympus AU 400 chemistry analyzer (Olympus, Tokyo, Japan).

Measurements of ethanol and creatinine

The ethanol content of the consumed beer and wine was measured using a routine headspace gas chromatographic procedure with a flame ionization detector. Creatinine in urine was determined via the Jaffé reaction, using the DRI® Creatinine-Detect® test (Microgenics, Passau, Germany) on a Hitachi 912 automatic analyzer (Roche, Basel, Switzerland).

Results

Results from ingestion experiments

EtG and EtS concentrations of < LOQs were determined in all urine samples before commencing the ingestion experiment. Maximum time (Δt) for EtG and EtS concentrations above different cutoffs and the numbers of positive urine samples after 24 h are summarized in Table 3. The data relating to nonalcoholic beer originates from a previous study [24]. Figure 1 shows the determined EtG (a) and EtS (c) concentrations within the range of the cutoffs versus time and the time curves of EtG 100 (b) and EtS 100 (d) concentrations normalized to creatinine concentrations of 100 mg/dl.

After drinking (24 to 27 h), EtG concentrations (cEtG) above 0.5 mg/l were determined in two urine samples only. The affected persons had consumed 0.2 l of white wine or 0.66 l of beer. None of the creatinine-normalized EtG concentrations exceeded 0.5 mg/l. In the urine samples of five (six with normalized EtG concentrations) participants, concentrations above 0.1 mg/l were determined in this time period. After consuming (24–27 h) 0.1 l of white wine or 0.33 l of beer, all measured EtG concentrations were below 0.1 mg/l.

EtS was detectable for 20.5–23.5 h after the consumption of 0.1 l of white wine or 0.33 l of beer. After drinking 0.2 l of white wine or 0.66 l of beer, EtS concentrations (cEtS)

Table 2 Personal data and breath alcohol content of the patients under withdrawal treatment

Number	Sex	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)	BrAC (‰)
U01	Male	42	182	73	22.0	0.85
U02	Male	54	178	70	22.1	2.29
U03	Male	30	188	92	26.0	2.8
U04	Male	49	–	–	–	2.1
U06	Male	43	180	67	20.7	2.6
U07	Female	55	158	60	24.0	1.8
U09	Male	39	180	82	25.3	3.08
U10	Male	46	181	90	27.5	1.7
U13	Female	-	170	68	23.5	3.13
U14	Male	37	172	77	26.0	1.35
U15	Female	39	–	–	–	1.23
U17	Male	39	185	75	21.9	2.98
U18	Female	42	150	62	27.6	1.8

BrAC breath alcohol content

above the LOD could be determined for 22.5 to >28.5 h. Creatinine normalization of the EtS concentrations had no effects on the window of detection.

Results from patients under withdrawal treatment

The urinary EtG and EtS concentrations of 13 patients heavily intoxicated by alcohol were determined over the first 36–132 h under withdrawal treatment. Figure 2 shows the measured EtG and EtS concentrations versus time within the range of the cutoffs. Twelve patients showed the highest EtG and EtS concentrations in the first samples which were collected right after admission for inpatient treatment, followed by considerably lower concentrations determined 12 h later. One patient (U02) showed an increase of EtG and EtS in urine after 12 h. It is very likely that this patient had consumed alcohol shortly before sample collection. In the urine samples of another patient (U08), EtG and EtS concentrations increased after 84 h. This could be explained by concealed consumption of alcohol.

After 36 h, 1 of 13 urine samples was tested negative for EtG (c_{EtG}<0.1 mg/l). Using a theoretical cutoff value of 0.5 mg/l, 4 out of 13 urine samples would have become negative after 24 h, and 8 out of 13, after 36 h. One twenty h after the first urine sample, EtG concentrations > LOQ (0.019 mg/l) could be detected in 2 out of 9 urine samples (0.03 and 0.13 mg/l).

After 24 and 36 h, EtS concentrations between 0.06 and 12.7 mg/l and 0.04 and 3.32 mg/l were determined, respectively. Concentrations below 0.1 mg/l were determined in 2 out of 13 urine samples after 24 h, and in 4 out of 13 samples after 36 h. EtS concentrations below 0.05 mg/l were only determined in 2 urine samples which had been collected after 36 h. After 120 h, EtS concentrations above

Table 3 Maximum time (Δt) for concentrations above different cutoffs and the numbers of positive samples after 24 h for EtG and EtS in urine

	Nonalcoholic beer	White wine		Beer	
	2.0–3.0 l	0.1 l	0.2 l	0.33 l	0.66 l
Δt (c_{EtG}>0.1 mg/l) (h)	13.0	22.0	>28.5	23.5	>28.0
Δt (c_{EtG} 100>0.1 mg/l) (h)	13.0	23.5	>28.5	23.5	>28.0
Δt (c_{EtS}>0.05 mg/l) (h)	12.8	11.8	26.5	20.5	>28.0
Δt (c_{EtS} 100 > 0.05 mg/l) (h)	11.7	14.5	23.5	19.5	>28.0
c_{EtG}>0.1 mg/l (t=24 h)	0/6	0/2	2/3	1/3	3/4
c_{EtG} 100 > 0.1 mg/l (t=24 h)	0/6	1/2	2/3	2/3	4/4
c_{EtG}>0.5 mg/l (t=24 h)	0/6	0/2	2/3	0/3	1/4
c_{EtG} 100 > 0.5 mg/l (t=24 h)	0/6	0/2	0/3	0/3	0/4
c_{EtS}>0.05 mg/l (t=24 h)	0/6	0/2	3/3	0/3	3/4
c_{EtS} 100 > 0.05 mg/l (t=24 h)	0/6	0/2	1/3	0/3	3/4
c_{EtS}>0.1 mg/l (t=24 h)	0/6	0/2	1/3	0/3	2/4
c_{EtS} 100 > 0.1 mg/l (t=24 h)	0/6	0/2	0/3	0/3	1/4

Concentrations above different cutoffs (c_{EtG} of >0.1 mg/l and >0.5 mg/l; c_{EtS} of >0.05 mg/l and >0.1 mg/l); c_{EtG} 100 and c_{EtS} 100 are the normalized EtG and EtS concentrations on a urinary creatinine content of 100 mg/dl

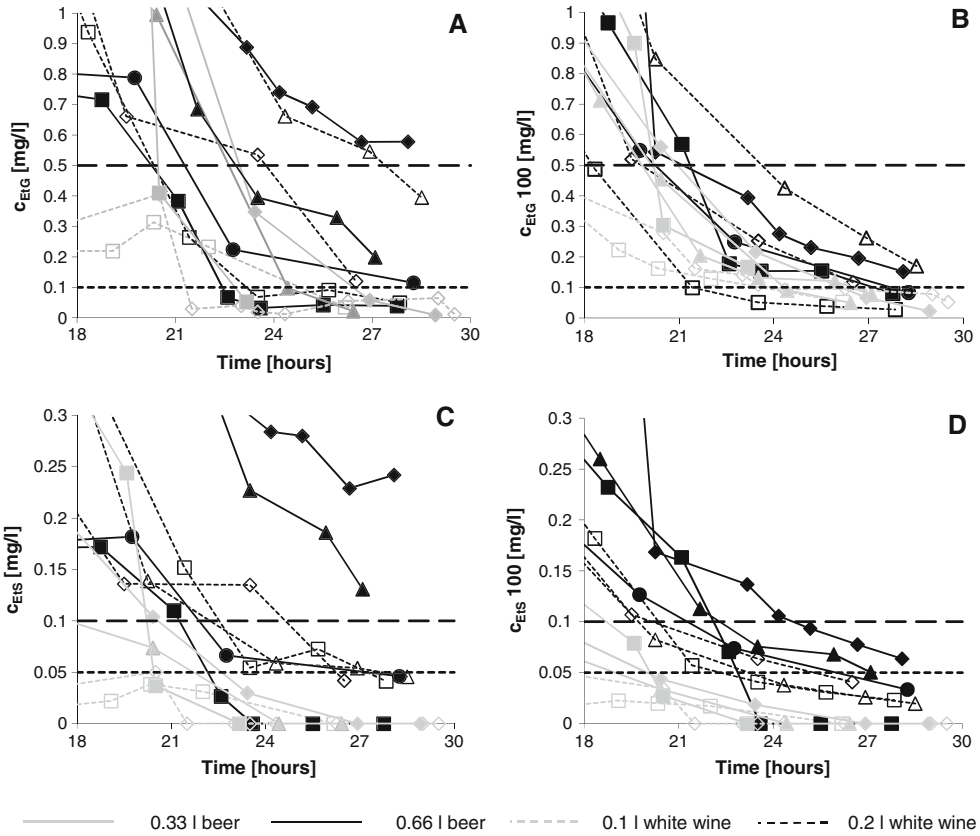

Fig. 1 Determined EtG (**a**) and EtS (**c**) concentrations in the range of the cutoffs and creatinine normalized ($c_{creatinine}$=100 mg/dl) EtG 100 (**b**) and EtS 100 (**d**) concentrations versus time

the LOQ (0.015 mg/l) were determined in six out of nine urine samples.

Results of the immunochemical determination of EtG

Urine samples (124) were additionally analyzed immunochemically. Sensitivity and specificity of the assay were calculated by SPSS on the basis of a receiver-operating characteristic. An EtG cutoff of 0.1 mg/l was adopted for the LC-MS/MS procedure. Using an immunoassay cutoff of 0.08 mg/l was the best compromise between sensitivity (98.6 %) and specificity (84.9 %) with an area under the curve of 0.985. Besides consistent results in 114 cases, 9 false positives and 1 false negative were registered for the immunoassay.

Discussion

Urine testing for EtG is widely used to verify recent alcohol intake and to monitor alcohol abstinence. First investigations describe EtG as an alcohol consumption marker which can be determined in urine for up to 80 h [37]. However, such a long time window for detection can only be achieved after the consumption of large quantities of alcohol. In the urine samples of some patients undergoing the first days of

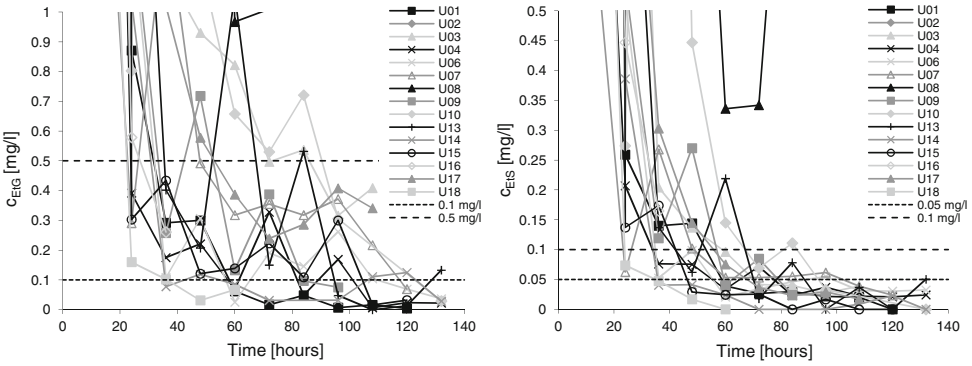

Fig. 2 Determined EtG (*left*) and EtS (*right*) concentrations in urine in the range of the cutoffs versus time of patient under withdrawal treatment

withdrawal treatment, EtG could be detected for even more than 120 h. Similar results were found by Helander et al. [15], who determined EtG concentrations above the applied clinical cutoff limit (0.5 mg/l) 40–130 h after admission to hospital.

The time window for detection of urinary EtG strongly depends on the quantity of the consumed alcohol. In the present studies, it has been shown that, 24 h after the consumption of small quantities of alcohol (0.33 l beer or 0.1 l white wine), all measured EtG concentrations were below 0.1 mg/l. Consistent results were found in four previous studies [4, 8, 11, 13], which include ingestion experiments with alcohol doses between 0.1 and 0.3 g/kg. EtG concentrations above the applied cutoffs (0.1 or 0.15 mg/l) could be detected for 6–25 h maximum. Wojcik et al. [8] concluded that using a 0.1 mg/l cutoff is not effective to detect low-dose alcohol consumption (0.25 g EtOH/kg) if the participants of abstinence programs are given 24 h of time to take the test.

This leads to the conclusion that determination of EtG in urine using 0.1 mg/l as cutoff value for EtG cannot prove strict alcohol abstinence in every case, especially if the participants are given 24 h time to take the test.

Proving strict abstinence would imply a lower cutoff value or a significantly shorter period of time to take the test. The latter is difficult to realize if participants of abstinence programs are in employment or have to travel far. Using lower cutoffs would increase the risk of false positive results due to unintentional consumption of alcohol.

Even EtG concentrations above 0.1 mg/l may be detectable in urine after consumption of food or beverages containing hidden amounts of alcohol or after intensive use of alcohol-containing cosmetics [10, 21, 24–29]. An excess of the cutoff was determined only for a limited time period which is considerable shorter than 24 h [24, 25, 28].

However, even unintentional consumption of alcohol is contrary to the requirement of strict abstinence. For this reason, participants of abstinence programs have to be informed about the hidden alcohol content of certain foods and beverages [12]. It needs to be clarified that consumption of large quantities of food and beverages, containing small amounts of hidden alcohol, may cause a higher absolute intake of ethanol than drinking one glass of wine or beer.

Higher cutoffs, e.g., 0.5 mg/l, which are still being discussed, are less suitable to check abstinence considering the results of these studies. Twenty-four h after the consumption of 0.66 l of beer or 0.2 l of wine, EtG concentrations of >0.5 mg/l were determined in only 2 out of 7 urine samples, and all normalized EtG concentrations were below 0.5 mg/l. Even 4 out of 16 strongly intoxicated patients would have been tested negative 24 h after commencing withdrawal treatment when using a cutoff of 0.5 mg/l.

It is remarkable that the maximum EtG concentration is much lower after drinking 2–3 l of alcohol-free beer than after consuming 0.1 l of white wine, even though a similar absolute amount of alcohol is consumed (Table 3). This may be the consequence of the notably different volumes of the drinks, which lead to a deviant excretion profile of urinary EtG. Høiseth et al. [22] explained similar results after comparative consumption of 1.8 g of alcohol in the form of nonalcoholic wine or vodka with different drinking periods.

Good results were achieved in the comparative determination of EtG concentrations of <0.5 mg/l immunochemically. Convergent results were found in 91.9 % of cases. Preliminary investigations require a small number of false negatives. High sensitivity (98.6 %) was achieved using a lower cutoff for the immunoassay (c_{EtG}=0.08 mg/l). The immunoassay used seems to be suitable for preliminary and semiquantitative determination of EtG in urine.

Hair analysis for EtG is another option to prove alcohol abstinence in Germany. Several studies have investigated the applicability of this alcohol metabolite as an abstinence marker in hair [38–41].

However, Kronstrand et al. [42] and Lees et al. [43] recently showed that a negative EtG result cannot prove strict alcohol abstinence. Even after daily consumption of 16 or 32 g alcohol over a period of 2 months, quantifiable EtG concentrations could not be determined in every hair sample. These results suggest that neither the determination of EtG in urine nor the analysis of EtG in hair is applicable to prove strict abstinence.

So far, only the EtG concentrations determined in urine and possible EtG cutoffs have been discussed. As already mentioned in the introduction, EtS appears to be more stable and thus may be the more reliable alcohol abstinence marker in urine. However, no cutoff for EtS in urine has been assessed yet. According to Wurst et al. [13], who performed a controlled consumption experiment, EtS is both earlier and longer detectable in urine than EtG. The final positive results for EtS (LOD 0.05 mg/l, LOQ 0.11 mg/l) were found 19.7–26.3 and 21.0–29.4 h after the intake of 9 and 18 g of alcohol, respectively. Similar results were found by Høiseth et al. [6] who determined EtS in urine (LOD 0.1 mg/l) for 25–39 h after consuming 0.5 g EtOH/kg.

Two possible cutoffs (0.05 and 0.1 mg/l) were tested using the data of this study and previous ones. Concentrations above 0.05 mg/l could be found for a maximum of 20.5 h after drinking 0.1 l of white wine or 0.33 l of beer. Consumption of 16.4 g (0.66 l of beer) or 23.1 g (0.2 l of wine) alcohol caused EtS values exceeding 0.05 mg/l in six out of seven urine samples after 24 h. After the same time period, EtS concentrations above 0.1 mg/l were measured in only three out of seven urine samples. EtS concentrations above 0.05 mg/l were detected in all urine samples of

patients under withdrawal treatment that were collected during the first 24 h.

On the basis of these two studies, it seems to be appropriate to use 0.05 mg/l as the cutoff to determine repeated consumption of alcohol for up to 24 h. The proposed value seems to be sufficiently low to avoid false positives, except during the first hours after unintentional consumption of alcohol. The determined median of the molar ratio of EtG and EtS concentrations (2.3), which is in good agreement with a previously published value [15], is consistent with this cutoff. However, proving strict abstinence is not possible. Caution is recommended when consuming EtS-containing beverages, for example, alcohol-free wine or grape juice. Previous studies showed that grape juice and nonalcoholic wines contain EtS that can be detected in urine for up to 20–27 h after consumption of 1.5 l of red grape juice or 2 l of white grape juice [22, 24].

The performed studies of course have some limitations. Due to the small number of study participants and missing information about the drinking habits of the patients undergoing withdrawal treatment, results cannot be considered representative. The introduced cutoff of 0.05 mg/l represents just an initial and preliminary proposal for discussion. Further research is required to verify this value.

Conclusion

Quantitative determination of EtG in urine is a common procedure to detect previous consumption of alcohol. However, the optimum cutoff for abstinence tests in urine is still being discussed controversially.

A compromise has to be found between avoiding false positives due to unintentional consumption of alcohol as well as false negatives caused by high cutoffs. The widely used EtG cutoff of 0.1 mg/l seems to be appropriate to determine repeated consumption of alcohol. The risk of getting a false positive result due to unintentional alcohol consumption is limited to a few hours. Using 0.5 mg/l as cutoff is not suitable for abstinence tests.

For EtS, no cutoff has been established so far. Based on the results of these studies, a cutoff of 0.05 mg/l is proposed for discussion. Under the given conditions, both tests are not suitable to prove strict abstinence.

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