

ETHYL GLUCURONIDE: A BIOMARKER TO IDENTIFY ALCOHOL USE BY HEALTH PROFESSIONALS RECOVERING FROM SUBSTANCE USE DISORDERS

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Abstract — **Aims:** Physicians recovering from substance-related disorders are usually allowed to return to practice if they agree to remain abstinent from drugs, including alcohol, and to undergo random urine testing. Over 9000 physicians are currently involved in such monitoring programs in the US. To date, it has been difficult to adequately monitor abstinence from alcohol due to the short half-life of alcohol and no other highly specific marker. Ethyl glucuronide (EtG), a direct metabolite of alcohol, offers an extended window for assessment of drinking status (up to 5 days). Our aim was to assess the potential value of EtG testing in abstinence-based monitoring programs. **Patients and methods:** Urine samples were obtained from 100 participants in a physician monitoring program and additional samples were subsequently obtained 'for cause', 'to verify positive urine alcohol, when drinking was denied' and 'in high risk individuals'. All participants had signed contracts agreeing to remain abstinent from mood-altering drugs, including alcohol, and had agreed to random urine testing. EtG was determined using LC/MS-MS in addition to standard testing. The main outcome measure were urine specimens positive for EtG versus those positive based on standard testing for alcohol and other drugs. **Results:** Among the initial 100 random samples collected, no sample was positive for alcohol using standard testing; however, seven were positive for EtG (0.5–196 mg/l), suggesting recent alcohol use. Subsequent EtG testing was performed clinically during the course of monitoring. Of the 18 tests performed to date, eight of eight tests performed 'for cause' were positive for EtG but negative for all other drugs including urine alcohol. All eight were confirmed positive by self reported drinking by the patient when confronted regarding the positive test result. Of six tests performed to 'confirm a positive urine alcohol' two were positive for EtG and confirmed positive by self reported drinking. For the other four samples, especially as two are from a diabetic, *in vitro* fermentation of ethanol is discussed. **Conclusions:** These data suggest that physicians in monitoring programs have a higher rate of unrecognized alcohol use than previously reported. Incorporation of EtG testing into alcohol abstinence monitoring can strengthen these programs.

INTRODUCTION

Substance abuse by medical practitioners is, by its very nature, a sensitive, but critical issue. The issue recently achieved news headline status following an outbreak of bloodstream infections transmitted by an addicted health professional in an intensive care unit (Ostrowsky *et al.*, 2002; Verghese, 2002). Reports have shown that substance-related disorders are as common among health professionals as, indeed, they are among the general population with a 10–15% lifetime prevalence (Brewster, 1986; Talbott, 1987; Anthony, 1992; Flaherty and Richman, 1993). Reports have shown that with treatment and long-term monitoring, the prognosis is excellent with >90% of health professionals with previous substance abuse disorders remaining abstinent at 5 years follow-up (Shore, 1987; Skipper, 1997), and that the public is protected. An unpublished online survey of state Physician Health Programs revealed a total of 9139 physicians in monitoring programs in the USA. Similar programs exist for monitoring other professionals such as attorneys, pilots, etc.

Regulatory boards are charged with overseeing and regulating licensees and, in turn, support and sanction Physician Health Programs to accomplish the tasks of early detection, confidential investigation and intervention, referral for evaluation and treatment, and monitoring. Relapse rates

amongst physicians participating in Physician Health Programs have been remarkably low, 1–3% per year (Shore, 1987; Alabama Physician Health Program Annual Report, 2003), a level that has been attributed to intensive long-term monitoring (Crowley, 1986). An alternative explanation for the reported low relapse rate might be associated with under-recognition by those monitoring the patients due to lack of availability of adequate objective tests.

Additionally, the previously reported high rate of suicide among physicians disciplined for substance-related disorders reported by Crawshaw (1980) has markedly decreased. Certainly other problems cause impairment (e.g. other mental illness, ageing, etc.) and many are remedial; however substance-related disorders are the most common and most treatable.

Monitoring in this population generally includes personal follow-up, worksite monitor reports, support-group attendance, and most importantly, random urine testing. Subject to full chain of custody procedures and sound methodology, the reliability of urine testing is high and few false-positive reports occur when positive screening tests are routinely confirmed by GC/MS or other confirmatory testing. Urine testing in general has become more prevalent across US worksites due to emergence of federally mandated drug testing programs. Millions of urine drug tests are now performed annually in the US.

More extensive lab test panels are utilized to monitor health professionals to detect the wider array of drugs available to and abused by this population. A 'health professional' panel typically includes the top 20–30 prescription drugs, and

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alcohol, most often abused by physicians. Many of the drugs that are popular among health professionals, including hydrocodone, oxycodone, meperidine, various benzodiazepines and stimulants (such as ritanserin), are reasonably well detected if tested for because of their long time-frame of detection in urine. Others, including fentanyl and ethanol, have relatively short half-lives and are difficult to detect. Fentanyl can be detected by hair testing, which can be obtained periodically. Ethanol however, the most common drug of choice among chemically dependent health professionals, e.g. 44% in Alabama (Alabama Physician Health Program Annual Report, 2003), is the least amenable to detection. More accurate testing for alcohol consumption is clearly needed.

The traditional state markers of alcohol consumption such as gamma-glutamyl-transpeptidase, mean corpuscular volume and carbohydrate deficient transferrin, reflect chronic consumption of higher amounts of alcohol and are, therefore, insensitive indicators of single or short term use. Furthermore, many currently used state markers are influenced by age, gender and a variety of substances and non-alcohol-associated diseases (Gilg and Soyka, 1997; Laposata, 1999). Urine alcohol is the most commonly used marker for routine monitoring of health professionals. However, because alcohol is rapidly metabolized over hours it is a relatively insensitive test to detect alcohol use. Additionally, because alcohol can be present in urine because of *in vitro* fermentation, false-positive tests for urine alcohol occur (Saady *et al.*, 1993). In contrast, ethyl glucuronide, EtG, a direct metabolite of ethanol, is only detected if alcohol is consumed, and remains present in urine well after the disappearance of ethanol itself. EtG appears to be a highly sensitive, specific, and reliable marker of recent (up to 5 days) alcohol intake (Kamil *et al.*, 1952; Jaakonmaki *et al.*, 1967; Kozu, 1973; Schmitt *et al.*, 1995, 1997; Wurst *et al.*, 1995, 1999a,b, 2000, 2002a,b, 2003a,b; Aderjan *et al.*, 1999; Nishikawa *et al.*, 1999; Dahl *et al.*, 2002; Goll *et al.*, 2002). Detection of EtG in urine, therefore, indicates recent alcohol consumption. Although there is a rough correlation between the amount of alcohol consumed and the level of EtG detected, the finding of EtG levels above cut-off values in urine simply indicates recent alcohol consumption. In this way the results are binary, indicating the presence of alcohol use, similar to positive tests for other illicit drugs (i.e. cocaine, opioids, etc.).

The formation of EtG via conjugation of ethanol with activated glucuronic acid in the presence of membrane-bound mitochondrial UDP glucuronyl transferase represents ~0.02% and 0.04% in humans (Dahl *et al.*, 2002; Goll *et al.*, 2002). The molecular formula of EtG is C₈H₁₄O₇ and the molecular weight is 222 g/mol. The melting point (decomposition temperature) is ~150°C. EtG is a non-volatile, water-soluble, stable marker. Shortly after intake of alcohol, EtG becomes positive (Wurst *et al.*, 1999, 2002a, 2003b; Dahl *et al.*, 2002) and is detectable up to 4 days following complete elimination of alcohol from the body (for review, see Wurst *et al.*, 2003b). Determination has been reported using GC/MS, LC/MS, LC/MS-MS and ELISA. More than 4000 samples from more than 1300 individuals have been tested for EtG by various research groups, including from the WHO/International Society for Biomedical Research on Alcoholism (ISBRA) collaborative study on biological state and trait markers of alcohol use and dependence. There has been no reported false-positive test for EtG using LC/MS/MS methods.

The purpose of the current study was to determine if EtG could identify instances of drinking that failed to be determined using standard urinalysis testing for alcohol.

PATIENTS AND METHODS

Patients

Primary screening of 100 subjects. One hundred initial urine samples were obtained randomly from 100 different healthcare professionals currently in monitoring. All had diagnoses of substance dependence and all had completed treatment and were participants in one of eight physician health programs from different states. Samples were obtained at a central laboratory that performs testing for various state programs. All state physician health programs included operate similarly and have similar policies, testing procedures, and monitoring contracts. No other inclusion criteria were applied and there was no record of participants' age or sex. Subjects were presumed to be at varying stages of time following treatment, as no selection of any subgroup was made. All had signed monitoring contracts and informed consent agreements regarding random testing for drugs of abuse, including alcohol. Investigators were blind to the names of these participants; therefore exact data regarding individual diagnoses, states from which the participants came, and how representative these 100 individuals were relative to the more than 9000 individuals in monitoring in the USA is not known. It is assumed, however, because they are a random sample, that they are not appreciably different from others in this group.

Clinical application in 12 physicians. Subsequent to the testing of the 100 samples above, 18 samples were obtained from a total of 12 physicians in an operational monitoring setting in Alabama. Selection for testing was based on one of three separate indications: i) eight samples were obtained 'for cause' (due to reports of suspected drinking), ii) six were obtained 'to verify a positive urine alcohol test when drinking was denied', and iii) four were obtained randomly in 'high risk individuals' with a history of frequent relapses. Data from these tests are included to demonstrate the early initial evidence of the value and utility of EtG testing. Use of EtG testing is rapidly increasing in these programs.

Ethics Committee

IRB review was waived by the Medical Association Ethics Committee.

Methods

Standard HHS rules were followed for specimen collection and chain of custody. To avoid risk of substitution or adulteration, laboratory personnel witnessed all urine test collections. The limit of determination (LOD) for determination of urinary alcohol was 0.02 g%. A 3 ml aliquot of each urine sample was frozen and sent for EtG determination. EtG testing was performed: i) at the Institute of Legal Medicine, University of Freiburg, Germany for the first 100 samples, and ii) subsequently by a commercial laboratory in the US.

For the EtG LC-MS/MS analysis at the Institute of Legal Medicine in Germany, a recently published method (Weinmann *et al.*, 2004) was used with minor modifications.

The LC-MS/MS system comprised an API 365 triple-quadrupole mass spectrometer fitted with a turboionspray interface (Applied Biosystems/Sciex, Langen, Germany) and coupled to a Shimadzu LC system (two pumps LC10AD Shimadzu, Duisburg, Germany). Analysis was performed by multi-reaction monitoring, using 221/75 amu for EtG and 226/75 amu for D₅-EtG (dwell times: 400 amu for each transition), with dummy transitions in between to eliminate the potential of cross-talk.

The EtG tests on the later 12 physicians performed at a commercial laboratory in the US, were done using similar technique as described above.

Other toxicology testing

All specimens, in addition to EtG testing, were analysed at Quest Diagnostics using an expanded 'health professionals panel'. Determination of urinary ethanol was performed as a screen by the standard enzymatic method using alcohol dehydrogenase (cut-off: 0.02 g%) and all positive tests were confirmed by gas chromatography (cut-off: 0.01 g%).

Sample preparation

To 0.2 ml urine sample 10 µl aqueous solution of internal standard (D₅-EtG, 10 µg/ml, Medichem, Germany) and 0.5 ml methanol were added. After centrifugation (10 min, 14 000 r.p.m. at 4°C) the supernatant was evaporated to dryness using a vacuum concentrator (Christ Alpha RVC, Osterode/ Germany). Redissolving and dilution was performed in relation to the creatinine concentration with 0.1% HCOOH (v/v); for creatinine concentrations <50 mg/dl, the sample was redissolved and diluted by factor 2, for creatinine concentrations 50–100 mg/dl by factor 4, for creatinine concentrations 100–200 mg/dl by factor 6, for creatinine concentrations >200 mg/dl by factor 8. An aliquot of 10 µl of the diluted sample was injected into the LC/MS/MS system.

Method validation

For the EtG test, method validation has been performed using a method based on linear regression (Funk *et al.*, 1991) with an α -error of 1% and a relative confidence interval of 33% ($k = 3$), using B.E.N. software [supplied by Arvecon/Walldorf, Germany, a standard program for method validation supported by the German Society of Forensic Toxicologists (GTFCh) for the detection of drugs of abuse in serum and urine samples in forensic cases]. The limit of detection of the method was 0.1 mg/l; the lower limit of quantification (LLOQ) was 0.3 mg/l.

RESULTS

None of the first 100 specimens were positive for alcohol, however, seven were positive for ethyl glucuronide at levels of between 0.5–196 mg/l. Results of EtG positive tests are shown in Table 1. Creatinine values of between 19.4 and 254.7 mg/dl were found. EtG/creatinine ratios were utilized to standardize all EtG values on creatinine 100, resulting in calculated UEtG 100 values and were between 0.2 and 93.8 mg/l.

Of the 18 tests performed so far in the monitoring program in Alabama, eight were 'for cause' due to complaints of suspected alcohol use, six to 'confirm positive urine alcohol

Table 1. Synopsis of results for those samples positive for ethyl glucuronide among the first 100 samples

Sample no.	UEtG [mg/l]	Creatinine [mg/l]	UEtG 100 [mg/dl]	Urinary ethanol	Other drugs tested positive
1	42	90.2	46.5	<LOD	None
2	1.3	24.9	5.2	<LOD	None
3	85	254.7	33.3	<LOD	None
4	196	208.8	93.8	<LOD	None
5	4.9	19.4	25.3	<LOD	None
6	4.1	185	2.2	<LOD	None
7	0.5	242.6	0.2	<LOD	None

UEtG: urinary ethyl glucuronide; UEtG 100: urinary EtG standardized for a creatinine of 100 mg/dl; LOD: limit of determination.

Table 2. Synopsis of 18 subsequent EtG tests performed clinically during monitoring

Patient	Age	Sex	Reason for testing	UEtG mg/l	Confirmed positive by patient
1	50	M	For cause	1.2	Yes
2	57	M	UAC.01 g%	0	No
3	53	M	For cause	2.2	Yes
3	53	M	For cause	8.1	Yes
4	46	M	For cause	12	Yes
5	55	M	High risk	0	No
6	54	M	For cause	0.8	Yes
6	54	M	For cause	1.6	Yes
7	46	M	For cause	>100	Yes
7	46	M	For cause	0.80	Yes
8	55	M	High risk	0	No
8	55	M	High risk	0	No
8	55	M	High risk	0	No
9	54	M	UAC.02 g%	17	Yes
10	36	M	UAC.06 g%	2.4	Yes
11	58	M	UAC.04 g%	0	No
12	46	M	UAC.02 g%	0	No
12	46	M	UAC.02 g%	0	No

UAC: Urine alcohol concentration; UEtG: urinary ethyl glucuronide.

tests' when alcohol use was denied, and four were performed in individuals routinely due to concern because of frequent previous relapses ('high risk'). Among these later tests, eight of eight tests performed 'for cause' were positive for EtG but negative for all other drugs, including alcohol, and all were confirmed positive by admission of drinking by the individual participant, two of six tests performed to 'confirm a positive urine alcohol' were positive and the two tests positive for EtG were confirmed positive by self reported drinking. None of the four tests in 'high risk' individuals were positive. All individuals with negative tests reported no ethanol intake (see Table 2).

DISCUSSION

The role of biological markers in alcoholism treatment has been recently addressed, with further mention that simply informing the patient that his or her blood will periodically be tested to evaluate treatment progress might, in fact, itself contribute to reducing relapse risk (Allen and Litten, 2001).

Thus, biomarkers of alcohol use may assist not only in assessing drinking status but in reducing it.

EtG has been demonstrated to be a useful marker of recent alcohol consumption because it is a direct metabolite of alcohol with good sensitivity and specificity and has a significantly longer time-frame of detection than urine alcohol. The data presented here suggest that health professionals in monitoring programs have a higher rate of alcohol use than previously reported. Among the 100 random samples reported here, the participants were anonymous and follow-up interviews to establish specificity were, therefore, not possible. High specificity has been established elsewhere (Wurst *et al.*, 2003b). In the subsequent group of 12 patients selected for testing utilizing EtG clinically it proved very effective. All positive tests in cases of testing 'for cause' were corroborated by self reported drinking. However, in the six cases with a positive UAC, only two were positive for EtG and confirmed by self reported alcohol intake. The other four need not necessarily be false negative tests for EtG, as a positive UAC does not necessarily prove an intake of ethanol. Due to fermentation of glucose, which is excreted by persons suffering from diabetes (like known for patient number 12, two samples), a significant rise of the UAC can occur at room temperature or elevated temperature in the pre-analytical period, e.g. when samples are not frozen when being delivered by postal service to the laboratory. In contrast to this possibility of *in vitro* formation of ethanol in urine, EtG is not known to be generated during the fermentation process. We therefore conclude that the positive results for UAC in patients 2 and 11 and negative results for EtG in the same samples not necessarily reflect false negatives for EtG but might be explained — also taking into consideration the negative self reports — by *in vitro* ethanol fermentation.

Recent preliminary anecdotal reports from numerous state physician health programs performing EtG testing suggest significant benefit: in Florida, for example, of 22 tests performed, 10 have been positive for EtG and all have been confirmed to be associated with admitted drinking episodes (personal communication with staff at the Florida Professional Recovery Network, 2004). In Alabama — as reported here — 18 EtG tests were performed over the past 6 months and appear useful as shown above.

Since the introduction of testing capability for EtG by laboratories in the USA in 2003, it is proving to be a valuable tool in these programs. The test has also been discussed for use in school testing programs, with pilots recovering from alcoholism and others. Because EtG testing is currently being performed using Liquid Chromatography Tandem Mass Spectroscopy (LC-MS/MS) the test is relatively expensive (up to US\$70), which limits its use. Development of an ELISA screening test for EtG is under development and should greatly reduce the cost. Some monitoring programs are attempting to include EtG in all urine panels. Others are using the test selectively, primarily in three settings: i) to confirm positive urine alcohol tests if alcohol use is denied, ii) 'for cause' when there is a heightened concern (such as following a report of suspected 'alcohol on the breath'), and iii) randomly and more routinely in 'high risk' individuals with a history of multiple relapses.

Questions regarding positive tests due to incidental exposure to alcohol [alcohol in food, over the counter medication (OTC meds; such as cough syrup), communion wine, mouthwash, etc.] are being asked. Because such a small fraction of consumed alcohol is metabolized to EtG, a significant amount of alcohol must be consumed for EtG to be detected in urine. However, cut-off levels for measuring EtG in urine have been set at between 100–250 $\mu\text{g/l}$ to eliminate detection of incidental minor exposure to alcohol. Additionally, it is recommended that individuals in abstinence monitoring be advised and agree to abstain, not only from overt alcohol use, but also from any alcohol use in food, OTC meds, communion wine, etc., to avoid claims of false-positive tests. Current analysis suggests that if the level of EtG in urine exceeds 500 $\mu\text{g/l}$, incidental exposure is extremely unlikely. In any event, if testing is positive, as with any laboratory test, clinical correlation is important.

Monitoring health professionals in recovery from substance-related disorders is necessary and important to protect patients and maintain high rates of success. By having reliable accurate testing programs the chances of early detection and assistance are optimized. Work-related monitoring with contingency contracting appears to be effective in reducing the rate of relapse. Use of better markers, such as the direct ethanol metabolite EtG, can help these programs maintain credibility and improve outcomes. The cumulative data suggest that ethyl glucuronide is a promising marker of recent alcohol use and will become an important part of the monitoring armamentarium. An ELISA (enzyme linked immunosorbent assay) screening test for EtG based on a monoclonal antibody is being developed (Mediagnost Inc., Germany) and, when available, will facilitate inclusion in routine testing panels. That EtG can be detected in various other body fluids including serum/blood, hair, and in tissue samples, may make the biomarker quite versatile in other situations where alcohol use must be determined some time after its occurrence (for review, see Wurst *et al.*, 2003b).

The complementary use of this marker together with other biological state markers and self reports in similar settings like the one described above (e.g. airline pilots, during pregnancy, workplace testing in safety sensitive jobs, methadone programs, etc.) is expected to lead to significant improvement in treatment outcome, therapy effectiveness, and considerable health, social and socio-economic benefits.

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