Prevalence of Ethyl Glucuronide and Ethyl Sulphate Among Patients Injured When Driving or at Work

Stig Tore Bogstrand1,2,3,#, Gudrun Høiseth1, Ingeborg Rossow4, Per Trygve Normann1 and Øivind Ekeberg5,6

1Division of Forensic Medicine and Drug Abuse Research, Norwegian Institute of Public Health, PO Box 4404, Nydalen, Oslo N-0403, Norway, 2Emergency Department, Division of Emergencies and Critical Care, Oslo University Hospital, Ullevaal, PO Box 4956 Nydalen, 0424 Oslo, Norway, 3Lovisenberg University College, Lovisenbergst. 15b, 0456 Oslo, Norway, 4Norwegian Institute for Alcohol and Drug Research, PO Box 565 Sentrum, N-0105 Oslo, Norway, 5Department of Acute Medicine, Oslo University Hospital Ullevaal, PO Box 4956 Nydalen, 0424 Oslo, Norway and 6Department of Behavioural Sciences in Medicine, Institute of Basic Medical Sciences, Faculty of Medicine, University of Oslo, Oslo, Norway

*Corresponding author: Division of Forensic Medicine and Drug Abuse Research, Norwegian Institute of Public Health, PO Box 4404, Nydalen, Oslo N-0403, Norway. Tel.: +47-21-07-78-22; E-mail: stigtore.bogstrand@fhi.no

(Received 20 May 2014; first review notified 10 July 2014; in revised form 20 August 2014; accepted 9 September 2014)

Abstract — Aims: Presence of EtG or EtS among patients injured when driving or at work may indicate that very low BAC or residual effects of alcohol at the time of the accident may be associated with increased accident risk. The aim of this study was to assess: whether the alcohol metabolites EtG and EtS were present in a sample of patients injured when driving or injured at work, even if their blood alcohol concentration was negative; and, if EtG and EtS were present, what characterized these patients. Methods: Blood samples from patients admitted for treatment of injuries at a Norwegian emergency department were tested for alcohol, EtG and EtS. All samples were also analysed for medicinal and illicit psychoactive substances. Results: One hundred and ninety-two injured patients who were admitted <12 h after injury were included in the study. EtG or EtS were the most prevalent substances in the sample (17%), and a substantial proportion of the patients who tested negative for all other substances tested positive for EtG or EtS (8%). These patients were older than the rest of the sample and drank alcohol more often, according to their self-report. Conclusion: EtG and EtS were prevalent among patients injured when driving or injured at work, including patients negative for all other substances. EtG and EtS should be included in future case–control studies of psychoactive substance use among injured patients to investigate the possible association between residual alcohol effects and injuries.

INTRODUCTION

Alcohol use is a significant risk factor for injuries because of its impairing effects on cognitive and motor functions (Taylor et al., 2010). Even moderate intake of alcohol and relatively low blood alcohol concentration (BAC) levels are associated with increased risk of injury in road traffic and other contexts where impaired cognitive and motor functions may be hazardous, such as complex work tasks involving dangerous machinery (Blomberg et al., 2009). Moreover, it is possible that alcohol use may play an indirect role in such injuries in terms of hangover effects; i.e. symptoms following a heavy drinking episode. A few studies in experimental settings have demonstrated psychomotor impairment in subjects with hangover, suggesting that hangover may also be a possible risk factor for injuries (Prat et al., 2008).

Studies documenting alcohol’s involvement in injuries are mostly based on measurements of BAC in blood samples or in expired air (breathalyser) or self-report drinking prior to injury (Cherpitel, 2007). Such measurements, may, however, represent an underestimate of the role of alcohol in injuries, for at least three reasons. First, BAC may be measured several hours after injury, and the impairing BAC level at the time of injury may no longer be detected by conventional BAC measurements. Second, injured persons may underreport alcohol intake prior to injury (Cherpitel et al., 2007). Third, the possible hangover effects from alcohol will not be detected by conventional BAC measurements.

An alternative way to assess the possible role of alcohol in injuries is to examine alcohol metabolites in injured persons. Ethyl glucuronide (EtG) and ethyl sulphate (EtS) are metabolites of alcohol which have been validated in several studies as markers for recent alcohol intake. They can be detected in blood for ~10 h after a small to moderate alcohol intake and up to 24 h after large, repeated alcohol intakes (Hoisteth et al., 2007a, 2009a). Consequently, a negative BAC and a positive EtG or EtS test in injured patients may indicate the involvement of alcohol, in terms of either acute effects of a low BAC or hangover effects. The hangover effects have been identified as performance deficits in several experimental and naturalistic studies. McKinney et al. found the effects similar to a BAC of 0.08% (McKinney et al., 2012). A paper by the Alcohol Hangover Research Group states that the impact of alcohol hangover on work performance and other daily activities can be profound, and more research is needed (Verster et al., 2010). But the literature on the prevalence of these alcohol metabolites in various population samples is still sparse. In a Norwegian study investigating the use of psychoactive substances in the workplace, 21% of the employees had consumed alcohol within the last 24 h, but none of these tested positive for alcohol. However, 2.1% tested positive for EtG in oral fluid with a cut-off value above 2.2 ng/ml, indicating an intake of >6 alcohol units the evening before (Gjerde et al., 2010). A study evaluating the usefulness of the EtG test among emergency room patients concluded that it was suitable for detecting recent alcohol intake (Neumann et al., 2008).

Impairment after alcohol ingestion when BAC is negative has previously been documented in some experimental studies, while other studies have not been able to demonstrate such impairment. Experimental studies performed on aircraft pilots reported attention deficits during hangover after high and moderate alcohol doses. In complex flight simulator tasks, more errors occurred during hangover. No effect was seen in studies with more simple performance tasks (Prat et al., 2008). Törnros and Laurell reported a hangover effect in a driving simulator the day after a mean alcohol concentrations of 176 mg%. The average blood alcohol concentration (BAC) was however 40 mg% when the effect was measured; no effect was reported at BAC = 0 (Törnros and Laurell, 1991). Other studies have reported that hangover after moderate alcohol
intake worsens precision, and hangover after a heavy intake also influences speed of response (Prat et al., 2008). In a case–control study of ski injuries, drinking the last drink within 12 h before skiing was associated with injury, which may be due to residual effects of alcohol (Cherpitel et al., 1998). Some types of work might require full psychomotor ability and may lead to injury if one is not focused, e.g. work on a construction site. But the literature on the matter is limited.

Work and traffic accidents are of particular interest as the current literature suggests that there are complex psychomotor tasks which are impaired not only by drug influence, but also by residual effects of alcohol (Prat et al., 2008). A high prevalence of EtG or EtS among patients injured in these kinds of accidents may indicate that very low BAC or residual effects of alcohol at the time of the accident may be associated with increased injury risk. However, no study has to our knowledge investigated the prevalence of EtG/EtS, in patients injured when driving and or at work. To investigate the matter further the present study explores if there were differences in demographic variables, injury time, and time from injury to hospital and prevalence of psychoactive substances EtG/EtS between patients injured when driving or at work. Then associations between patients in both groups positive for EtG/EtS and the same variables were tested, along with self-reported alcohol use. More specifically we wanted to:

- Assess whether the alcohol metabolites EtG and EtS were present in a sample of patients injured in traffic and workplace accidents even when BAC was negative, and if so, what characterized these patients.

MATERIAL AND METHODS

Setting and participants

Cross-sectional data from patients admitted to the emergency department of Oslo University Hospital, Ullevål, were collected consecutively over a 1-year period. Approximately 26,000 patients are admitted per year to this emergency department, which is also a trauma centre delivering health care to a population of ~2.5 million people in and around the city of Oslo. In addition, the hospital has a primary catchment area of five city sectors. All injured patients 18 years or above admitted to the hospital because of accidents, violence or self-inflicted injuries were asked to participate in the study (see flow chart: Fig. 1). Patients were not asked for study participation if they did not understand Norwegian, were severely psychotic, or mentally retarded or if, for other reasons, they could not give informed consent. If it was not possible to get an informed consent in the emergency department, a blood sample was obtained and the patients were asked to give informed consent later during the hospital stay. If such consent was not obtained, the blood samples were destroyed. The patients who were not asked for study participation later during hospital stay were either too severely injured on admission, or they were very slightly or not at all injured and discharged within <6 h of observation. The study population for this study is a sub-sample, consisting of all patients injured when driving or at work and admitted within 12 h of injury. Patients arriving later than 12 h (and up to several days) after the injury were excluded, because they could have consumed alcohol after the injury and this would have compromised interpretations of BAC and EtG/EtS findings.

Data collection and data sources

Presence of psychoactive substances was tested by analysing the blood samples for alcohol and other impairing substances associated with increased injury risk (Morland, 2000) and presence of EtG and EtS was tested only for this sub-sample of patients injured in traffic or at work. All substances were initially screened for and confirmed in blood by the Department of Forensic Medicine and Drug Abuse Research at the Norwegian Institute of Public Health (NIPH). The blood sample analysis was performed according to a previously published method (Hoiseth et al., 2007b). The sample preparation was performed according to the reference, and included protein precipitation with cold methanol followed by minimum 10 min at −20°C, centrifugation and evaporation of the supernatant to dryness. The residue was dissolved in acetonitrile/formic acid (1/99) followed by 2 min at −20°C, centrifugation and transfer of the supernatant. The chromatographic conditions were modified from the details given in the reference. Three μl was injected on a HSS T3 column (1.8 μm, 2.1 × 100 mm) and HSS T3 guard-column (1.8 μm, 2.1 × 5 mm) from Waters corp., Milford, MA, USA. The MS/MS instrument (Waters Quattro Premier XE) with electrospray ionization (ESI) was operated in negative mode for detection of EtS, EtS-d₅, EtG and EtG-d₅, at the following mass to charge ratios: m/z 124.9, 129.9, 220.9 and 225.9. Two transitions were monitored for EtG and EtS. Patient characteristics were obtained by questionnaire as soon after hospital admission as possible. Those patients who were not able to complete the questionnaire themselves were interviewed by an emergency department nurse. The data were collected for research purposes only, and could not be used for e.g. prosecution.

Fig. 1. Flow chart of patient participation.
The police took separate samples if they suspected impaired driving. All results from the study were stored in a de-identified research database at the NIPH; no results of single cases were reported back to the hospital.

**Variables**

The cut-off value for Ethanol (EtG) was 0.03 mg/l and for EtS was 0.006 mg/l. In the analyses we have applied a single dichotomous variable indicating the presence of EtG/EtS. BAC was also dichotomized and a cut-off value was set at 0.01%. The cut-off values for the other psychoactive substances (e.g. hypnotics, sedatives, cannabis and other illicit drugs) were set at a detection level and the details have been published in an earlier article (Bogstrand et al., 2011). We applied a dichotomous variable indicating presence or absence of any of these substances. A positive alcohol or drug screen does, however, not necessarily indicate clinical impairment.

Type of injury separated patients injured when driving and patients injured at work. Patient characteristics comprised age, gender, and self-reported drinking frequency and intoxication frequency in the previous year. The latter two variables were on a semi-continuous scale, with seven categories ranging from ‘None’ to ‘Several times a week’. For reasons of confidentiality, more severely injured patients included at the hospital wards after emergency treatment were not asked these questions, and the number of internal missing observations for these variables was, therefore, significant. These variables were also dichotomized, separating those who reported drinking/becoming intoxicated 2–3 times a month or more often from those who reported such behaviour less frequently or not at all.

**Statistical analyses**

Associations between categorical variables were analysed in bi-variate cross tables. Chi-square statistics were used to assess statistical significance. Fisher’s exact test was used to assess statistical significance in 2 × 2 tables where the expected count in one cell was less than five. Mean values and standard deviation (SD) were reported for continuous variables that were normally distributed, and statistical significance was assessed by Students t-test. For continuous variables that were not normally distributed median values and interquartile range (IQR) were reported and the Mann–Whitney test was used to assess statistical significance. For EtG and EtS concentrations and maximum- minimum values were reported. PASW statistics 20 (IBM SPSS) was used for statistical analysis. The level of significance was set at P < 0.05.

**Ethics**

All patients who were invited to participate were informed about the project verbally as well as in writing and were asked to give written informed consent. Patients were also informed that they could withdraw from the project at any time during data collection. The Data Inspectorate and the Regional Ethics Committee in Norway approved the study.

**RESULTS**

**Participants**

Of the 2779 injured patients 18 years and older who were admitted to the hospital during the 12 month study period, 661 (24%) were not asked for study participation. As described in the methods section they were either too severely injured to be asked about participation, or slightly injured or not injured at all and discharged before they could be asked about study participation. A total of 2118 patients were invited to participate in the study and of these, only 158 (7%) refused to participate, (Fig. 1). Of the 1960 participating patients, there were 1272 patients who were admitted <12 h after injury, 98 of these were patients injured when driving and 94 were patients injured at work. A total of 192 injured patients who were admitted <12 h after injury were therefore included in the study (Fig. 1).

The mean time from injury to blood sample was 2.5 h (SD: 2.1). The majority of patients were men (81%): 75% of the patients injured when driving and 88% of the patients injured at work (Table 1). The mean age of the patients injured when driving was 39.8 years (SD: 18.1) and for patients injured at work was 41.2 (SD: 13.5) (Table 1). Other comparisons of patients injured when driving and patients injured at work, showed that the former group: had their blood samples

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**Table 1. Bi-variate associations between patients injured when driving or patients injured at work and demographic variables, time from injury to hospital, injury time and prevalence of psychoactive substances, EtG and EtS (n = 192)**

<table>
<thead>
<tr>
<th></th>
<th>Injured when driving (n = 98)</th>
<th>Injured at work (n = 94)</th>
<th>Total (n = 192)</th>
<th>P-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, % (n)</td>
<td>75 (73)</td>
<td>88 (83)</td>
<td>81 (156)</td>
<td>0.01</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>39.8 (18.1)</td>
<td>41.1 (13.5)</td>
<td>41 (15.9)</td>
<td>0.57</td>
</tr>
<tr>
<td>Time from injury to blood sample, mean hours (SD)</td>
<td>2.1 (1.7)</td>
<td>3.0 (2.3)</td>
<td>2.5 (2.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>Weekend, % (n)</td>
<td>39 (38)</td>
<td>27 (25)</td>
<td>33 (63)</td>
<td>0.07</td>
</tr>
<tr>
<td>Injury at night (20:00–08:00 hours), % (n)</td>
<td>37 (36)</td>
<td>18 (17)</td>
<td>28 (53)</td>
<td>0.004</td>
</tr>
<tr>
<td>Prevalence of psychoactive substances</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative, % (n)</td>
<td>75 (73)</td>
<td>90 (85)</td>
<td>82 (158)</td>
<td>0.05</td>
</tr>
<tr>
<td>Alcohol, % (n)</td>
<td>12 (12)</td>
<td>2 (2)</td>
<td>7 (14)</td>
<td></td>
</tr>
<tr>
<td>Medicinal drugs, % (n)</td>
<td>13 (13)</td>
<td>4 (4)</td>
<td>9 (17)</td>
<td></td>
</tr>
<tr>
<td>Illicit drugs, % (n)</td>
<td>11 (11)</td>
<td>4 (4)</td>
<td>8 (15)</td>
<td></td>
</tr>
<tr>
<td>Combinations, % (n)</td>
<td>9 (9)</td>
<td>1 (1)</td>
<td>5 (10)</td>
<td></td>
</tr>
<tr>
<td>Prevalence of EtG and EtS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total, % (n)</td>
<td>21 (21)</td>
<td>13 (12)</td>
<td>17 (33)</td>
<td>0.11</td>
</tr>
<tr>
<td>Combined with alcohol, % (n)</td>
<td>12 (12)</td>
<td>2 (2)</td>
<td>7 (14)</td>
<td>0.007</td>
</tr>
<tr>
<td>BAC neg, % (n)</td>
<td>9 (9)</td>
<td>11 (10)</td>
<td>10 (19)</td>
<td>0.74</td>
</tr>
<tr>
<td>All substances neg, % (n)</td>
<td>8 (8)</td>
<td>9 (8)</td>
<td>8 (16)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

<sup>a</sup>Statistical test of significance: Pearson chi-square test for categorical values, and Students t-test—test for continuous variables.
been intoxicated 2-6 h before injury in the 6-h prior to the injury. They were more statistically significantly older. None of the EtG/EtS positive patients who tested positive for alcohol and other substances, had the following characteristics: they were statistically significantly older and positive for other psychoactive substances than those injured at work (15%). Correspondingly, a larger proportion of patients injured when driving were more likely to have a positive EtG/EtS screen (21%) than those injured at work (13%).

Characteristics of patients testing positive for EtG/EtS
Compared with the patients negative for all substances, those who tested positive for EtG/EtS and negative for alcohol and other substances, had the following characteristics: they were statistically significantly older. None of the EtG/EtS positive patients who were asked about alcohol use, reported any alcohol intake in the 6-h prior to the injury. They were more likely to report an intake >2–3 times a month of alcohol in the last 12 months. None of these patients reported that they had been intoxicated 2–3 times a month or more frequently in the last 12 months (Table 2).

EtG and EtS concentrations
Of the 16 patients who were EtG/EtS positive and negative for alcohol and other substances, 2 were positive for EtG alone and 10 were positive for EtS alone. The median blood concentrations of EtG and EtS in these patients were 0.06 and 0.03 mg/l, respectively. Among the EtG/EtS positive patients who also screened positive for alcohol and/or other substances, the mean concentrations were 1.2 mg/l for EtG and 0.7 mg/l for EtS (Table 3). The difference in concentration between the patients positive and negative for other substances was significant for both EtG and EtS.

DISCUSSION
Among the patients injured when driving or at work, EtG/EtS was found more often than alcohol or any other psychoactive substance, and a non-negligible proportion of the patients who tested negative for alcohol and other substances tested positive for EtG and/or EtS. These patients were older and reported drinking alcohol more often, but none of them reported to have been drinking in the 6 h prior to the injury.

Few studies have previously used prevalence of EtG and EtS among injured patients to detect earlier alcohol ingestion and possible hangover symptoms. One study among subcritically injured patients recommends the use of EtG to detect recent alcohol consumption also among BAC negative patients (Neumann et al., 2008). We could have asked whether the EtG/EtS positive patients in our study showed impairment due to hangover that could have caused their injuries. This is especially important in patients who are negative for all other substances, including alcohol, as hangover symptoms might be the only drug-related impairment in this group.

The detection of EtG/EtS in blood indicates ingestion of alcohol within the last 24 h, even if large or repeated doses of alcohol were ingested. In the group of subjects negative for all other substances, the highest EtG and EtS values indicate...
ingestion of about 8 units of alcohol within the last 10 h, according to calculations from earlier publications (Hoiseth et al., 2007a, 2009b; Lostia et al., 2013). In such a situation, hangover effects have been documented (Prat et al., 2008; Stephens et al., 2008; McKinney et al., 2012). For the rest of the patients negative for all other substances, a smaller alcohol intake, or a longer time since last ingestion, is more likely. We have not found studies measuring EtG or EtS and performance deficit. Prevalence of alcohol use among Norwegian workers and drivers in normal traffic is very low (Gjerde et al., 2008, 2010; Lund et al., 2011). We have no data on EtG or EtS concentrations among drivers in normal traffic, but the prevalence among workers was very low (Gjerde et al., 2010). The difference in prevalence of EtG among workers at the workplace in the study by Gjerde et al. (2.1%) and EtG and EtS among injured workers (13%), calls for a further investigation of the association between injuries and residual effects of alcohol.

The high prevalence of EtG and EtS relative to other psychoactive substances confirms the usefulness of EtG and EtS in studying alcohol intake among patients who last imbibed alcohol some time before sample collection. The interpretation of the findings is, however, more difficult. Accidents are often multicausal, with several factors interacting (Holder et al., 2001). In, for example, a traffic accident a driver might have impaired driving skills, but there might be other factors like a slippery road or bad weather conditions which co-occurs. To control for other factors a case–control design is preferable. As the study has no control group, it is not possible to assess if there is an increased injury risk associated with a positive EtG or EtS test, when other risk increasing factors are controlled for. As described above, some studies indicate that residual effects of alcohol may aggravate psychomotor performance, and thus lead to injury. But these studies have some major limitations: experimental studies of hangover effects have problems with blinding and naturalistic alcohol consumption studies have problems with expectancy effects from non-blinded participants (Stephens et al., 2008). To investigate this further a case–control study which tests for EtG and EtS, along with other psychoactive substances, should be the next step to investigate whether residual effects of alcohol consumption increase the risk of injury.

Strengths and limitations
The study has several strengths. The dataset comprises both workplace and car injuries where a comprehensive analysis of psychoactive substances has been performed. The participation rate is good and the laboratory analysis has been undertaken in an accredited forensic laboratory, using high quality substance-specific chromatographic methods. Another strength is that the patients were included during a whole year at a trauma centre.

Some refused to participate, and other patients were not possible to invite to the study. Non-participation may have biased the findings; however, we have no information on those not included in the study, which implies that assessment of magnitude and direction of a possible bias is not feasible. A limitation is the lack of control group. A possible association between injury and residual effects of alcohol cannot be assessed. The number of participants is relatively small and, owing to the low prevalence of EtG and EtS alone, the number of positive cases is low. Those patients who were not asked about drinking behaviour were severely injured, and if the findings related to self-reported alcohol consumption are contingent upon degree of injury severity, these findings cannot be generalized to severely injured patients. Another possible limitation is that the study cohort is from one hospital only, even though it is the major trauma centre in the region. Therefore, the findings cannot be generalized, without reservation, to other hospitals or outpatient emergency units. We have no data to suggest the direction of the possible bias. We consider, however, that the findings can be generalized to other major trauma hospitals at least in Scandinavia.

Implications
While many factors contribute to injuries residual, effects of alcohol may be among the preventable factors. It is therefore important to further investigate whether residual effects of alcohol may increase injury risk. This was to the best of our knowledge the first prevalence study of EtG and EtS in injured patients treated in hospital. Although several experimental studies have found impairing effects of hangover, many of these studies had methodological problems. An epidemiological approach would overcome the problems of experimental studies, especially with blinding. It is important, however, that a comprehensive drug screen is performed along with an EtG and EtS analysis because the combined use of psychoactive substances is widespread. It is therefore vital to analyse for all possible psychoactive substance to ensure that other psychoactive substances are not attributed to a positive EtG or EtS test. Future case–control studies of psychoactive substances in traffic should test for EtG or EtS to investigate the residual effects of alcohol.

CONCLUSION
EtG and EtS were prevalent among patients injured when driving and patients injured at work, even when BAC was negative. The patients positive for EtG and EtS were significantly older than other patients. EtG and EtS should be included in future case–control studies of psychoactive substance use among injured patients to investigate the possible association between residual alcohol effects and injuries. Whether hangover effects increase the risk of such accidents also needs attention in future studies.

Acknowledgements — The authors thank the staff at the emergency department Ullevål for all help with the data collection. We also thank the staff at Division of Forensic Medicine and Drug Abuse of NIPH for analysis of alcohol and drugs in blood samples and the Department of Biostatistics, Epidemiology and Health Economics at Oslo University Hospital for statistical advice.

Funding — The Norwegian Directorate of Health provided funding for the data collection. They had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Conflict of interest statement. None declared.

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