Use of Psychoactive Medicines and Drugs as a Cause of Road Trauma

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Keywords
Alcohol, drugs, injury, medicines, risk

Abstract
This article deals with the feasibility of a case-control design for determining the relative injury risk of motorists who have used alcohol, and/or illicit drugs, and/or medicines. Methods of data collection are presented, as well as analytical and statistical methods. Preliminary study results indicate that the use of illicit drugs by Dutch motorists is rapidly growing. Increased risk of road trauma (p <0.05) was assessed for single use of benzodiazepines or of alcohol, when resulting in a BAC between 0.5 and 1.3 g/L. High relative risk factors were assessed for combinations of several drugs and for BACs over 1.3 g/L. An extremely high risk factor was assessed for combined use of drugs and alcohol (generally resulting in high BACs). No enhanced risk was (yet) assessed for single use of alcohol resulting in a BAC between 0.2 and 0.5 g/L, and for single use of cannabis, amphetamines, cocaine, tricyclic antidepressants or opiates. Only for single opiate use, an odds ratio of more than 1 was found; this result, however, was not statistically significant.

Introduction
The dose-related accident risk of alcohol use was determined in several well-designed case-control studies, especially the well-known Grand Rapids Study (1). A similar study on the accident risk of the use of other psychoactive substances, however, has not yet been conducted. Apart from methodological and analytical reasons, an obvious reason for that is the high cost of such a study. Previous studies aimed at assessing the risk of driving under the influence of psychoactive substances other than alcohol, had important limitations. A lot of experimental research has been conducted in laboratory settings, using small numbers of volunteers. These studies measured the effects of controlled doses of psychoactive substances on psychomotor skills, supposedly relevant for driving. Most of these studies regarded prescription drugs. The results varied widely and provided only rough indications of the effects on accident or injury risk. Experiments in driving simulators, or even with instrumented cars in real traffic, made it possible to assess the effects on one or more aspects of the driving task, e.g. course holding (2), but the translation of these results into risk factors is difficult. Epidemiological research is more sparse and was often directed to the prevalence of drugs in either non-injured (3,4) or injured drivers (5), which made it impossible to determine risk factors. Case-control studies often included a very limited number of psychoactive substances, either of a licit or an illicit nature. Furthermore, in none of these studies did the control group consist of
drivers who were not involved in an accident. As a substitute for a proper control group, for instance, the whole population of a geographical area (6,7) or non-trauma hospital in-patients (8) were used.

Some researchers tried to overcome the control group problem by using a case-crossover design, as in the so-called culpability studies of (fatally) injured drivers (9,10,11). Important limitations of this type of study are the generally small numbers of subjects, and subjective elements which are involved in evaluating culpability.

In May 2000, SWOV and the Utrecht Institute for Pharmaceutical Sciences started a feasibility study, preceding a large-scale case-control study in the framework of the EU-project IMMORTAL (Impaired Motorists, Methods Of Roadside Testing and Assessment for Licensing), which started in January 2002.

Methods
A prospective case-control study was conducted to determine the relationship between the use of psychoactive substances and road trauma. Cases and controls were selected over a 15-month period, from May 2000 until August 2001. The study was conducted in the town of Tilburg and surroundings, covering a population of approximately 350,000 inhabitants. The Medical Ethics Committee of the St. Elisabeth Hospital approved the study protocol.

Body fluids of both cases and controls were tested for the presence of alcohol, cannabis, opiates, amphetamines, benzodiazepines, tricyclic antidepressants, and barbiturates. The relative risk of the use of these psychoactive substances was estimated by comparing the prevalence of these substances in cases and controls.

Cases
Potential cases were seriously injured motorists who were admitted to the emergency department of the St. Elisabeth Hospital. An index date was defined for each case as the calendar date at which the accident had happened. Urine and/or blood samples were taken on admission. Patients were defined as exposed to a drug when the laboratory test for a substance was positive. Medical and ambulance records were examined to control for drugs administered during transport and at the emergency department. When urine or blood samples were positive for drugs administered during transport or in the emergency department before taking the matrix, the samples were considered negative for these drugs.

Information on injuries of the case patients was obtained from medical records and records from the ambulance personnel. The doctors at the emergency department were trained to fill in a detailed questionnaire about the crash circumstances. The severity of injuries was graded according to the Injury Severity Scale (ISS).

All case patients, or their legal relatives, were asked for informed consent to participate in the study. If informed consent was not obtained during hospital admission, patients or their legal representatives were approached afterwards by mail. All data were processed anonymously.

Controls
During 20 roadside survey sessions, motorists were taken at random from moving traffic in the Tilburg police district, which covers the catchment area of the St. Elisabeth Hospital. In order to be able to construct a representative control sample, the week was systematically divided into 28 consecutive six-hour periods. Each of the 20 roadside survey sessions that were conducted, covered such a six-hour period. For the sake of statistical analysis, the original 28 six-hour periods were next aggregated into eight day/time categories, which were supposed to be more or less homogeneous with respect to traffic volume and substance use. These eight categories were:

1. the five weekday mornings (Monday to Friday), from 4 am till 10 am;
2. the five weekday ‘afternoons’ (Monday to Friday), from 10 am till 4 pm;
3. the four weekday ‘evenings’ (Monday to Thursday), from 4 pm till 10 pm;
4. the four weekday nights (Monday to Thursday), from 10 pm till 4 am;
5. the two weekend mornings (Saturday and Sunday), from 4 am till 10 am;
6. the two weekend ‘afternoons’ (Saturday and Sunday), from 10 am till 4 pm;
7. the three weekend ‘evenings’ (Friday to Sunday), from 4 pm till 10 pm; and
8. the three weekend nights (Friday to Sunday), from 10 pm till 4 am.

Motorists were stopped by the police and asked by researchers to participate in the study on a voluntary basis. The survey sessions were combined with normal police enforcement activities regarding drink-driving. During each survey session, four different research locations along main roads in the Tilburg police district were visited. The frequent change of location was intended to minimize the predictability of the alcohol controls with respect to place and time.

If the selected motorists agreed to cooperate, they were interviewed on their drug and medicine use and subsequently requested to produce a urine specimen. If they were not able or willing to do so, they were requested to deliver a blood specimen. A trained research nurse performed the venapuncture. Subjects who delivered a urine or blood specimen, received a small reward of 5 Euro.

Interviewing and sampling of body fluids took place in a specially equipped mobile research unit with private toilet. After the interview and the urine or blood sampling, all subjects were breath-tested for alcohol by a police officer, using a Dräger Alcotest 7410 Plus screening device. The breath test was compulsory for all motorists who were stopped by the police. Data collection also comprised date and time of selection, gender and age of the subject, and signs of intoxication.

**Analysis of body fluids**

Urine samples were screened at the Dutch Laboratory for Drugs Doping, Tilburg, by Enzyme Multiplied Immunoassay Technique (EMIT® II Plus). This technique is based on competition for drug antibody binding sites. For benzodiazepines a special high sensitivity protocol was used with on-line deglucuronidation. EMIT® II Plus ethanol assay is based on oxidation of ethanol in presence of alcoholdehydrogenase (ADH) with NAD to acetaldehyde. Samples were considered positive when the screening result was higher than the cut-off value mentioned in the SAMHSA guidelines for drug of abuse testing. Positive screening results for amphetamines and opiates were confirmed with appropriate gas chromatography/mass spectrometry (GC/MS) techniques. Using these techniques allowed to distinguish between amphetamine, methamphetamine, MDA, MDEA and MDMA. For opiates, GC/MS-confirmation allowed to distinguish between codeine, morphine and 6-monoacetylmorphine (heroin). Furthermore, confirmation by GC/MS excluded the risk of false-positive results.

Drug screening in serum was performed by the Dutch Forensic Institute (NFI), Rijswijk. Screening for opiates and cannabis was performed by Cozart® Enzyme ImmunoAssay (EIA), which is based on competition for drug antibody binding sites. Confirmation of opiates (codeine, morphine, 6-monoacetylmorphine (6-MAM) and normorfine) and cannabis (delta-9-tetrahydrocannabinol, 11-hydroxy-delta-9-tetrahydrocannabinol and 9-carboxy-11-nor-delta-9-tetrahydrocannabinol) was performed with GC/MS after solid phase extraction. Screening for the other drugs and pharmaceuticals was performed with high-performance liquid chromatography (HPLC) after solid phase extraction.

**Statistical analysis**

The relative risk of psychoactive substances was determined by comparing their prevalence in the experimental group with their prevalence in the weighted control sample, using a univariate logistic regression model in SPSS. Odds ratios were computed by relating subjects who had been tested positive for a substance or a combination of different substances, to subjects who had been tested negative for all substances. A 5% probability level ($p < 0.05$) was used for significance.
Odds ratios may also be computed by relating subjects who had been tested positive for a substance, regardless of the combination with other substances, to subjects who had been tested negative for that particular substance, regardless of their use of other substances. In that case, the effect of the substance on a population is determined, rather than the effect on a subject. The latter, however, is the goal of the IMMORTAL project.

Results
During the study period, a total of 112 evaluable cases of injured motorists were admitted to the emergency department of the St. Elisabeth Hospital. The relatives of two deceased patients refused consent; these two cases were excluded from the analysis. For 39.1% of the valid cases, a urine sample was available for analysis; for the other 60.9%, a blood sample. During the same period, a random sample of 1,029 motorists were stopped by the police and asked to participate in the study. Of these motorists, 20.7% did not deliver a specimen of a body fluid. Of 816 specimens, 84.8% consisted of urine and 15.2% of blood.

When compared to the non-response group, women aged 25-34 years were slightly under-represented in the response group, whereas men and woman of 50 years and older were slightly over-represented. With respect to alcohol use and self-reported use of other psychoactive substances, the response group was not significantly different from the non-response group. Based on these findings, there is no reason to suppose that the response group was selective with regard to the use of alcohol or illicit drugs. Users of prescription drugs, however, might be slightly over-represented in the response group, given the slight over-representation of older drivers. Furthermore, the unweighted control sample cannot be considered to be representative of all motorists who participated in road traffic in the Tilburg police district at all days of the week and all times of the day, since the sample distribution over different times and days was not equal to the distribution of traffic volumes. The reason for this is the more or less constant sampling capacity of the research team, regardless of the strongly varying traffic volumes, combined with a quite understandable preference of the police for enforcement activities during high-risk hours, i.e. the nighttime hours with low traffic volumes. In order to make the control sample representative, it was weighted on the basis of trip data that was collected over 1999 and 2000 by the Dutch Central Bureau of Statistics (CBS). Since no survey sessions were conducted during day/time categories 1 (weekday mornings) and 5 (weekend mornings), these categories were combined with categories 3 (weekday evenings) and 8 (weekend nights), respectively (Table 1).

Table 1: Comparison between day/time-distribution of the control sample of motorists and the CBS-sample of trips.

<table>
<thead>
<tr>
<th>Day/time categories</th>
<th>Distribution of control sample</th>
<th>Distribution of CBS-sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+3</td>
<td>14.9%</td>
<td>34.3%</td>
</tr>
<tr>
<td>2</td>
<td>18.4%</td>
<td>25.6%</td>
</tr>
<tr>
<td>4</td>
<td>16.5%</td>
<td>3.2%</td>
</tr>
<tr>
<td>5+8</td>
<td>24.3%</td>
<td>7.5%</td>
</tr>
<tr>
<td>6</td>
<td>11.2%</td>
<td>12.8%</td>
</tr>
<tr>
<td>7</td>
<td>14.7%</td>
<td>16.6%</td>
</tr>
</tbody>
</table>

The comparison shows that especially the nighttime hours were overrepresented in the control sample. Drink-driving is strongly concentrated in these hours. As a consequence, drink-driving was overrepresented in the unweighted control sample. This problem was solved by weighting.

Table 2 shows the distribution of psychoactive substances for cases and for the weighted control sample, together with the results of logistic regression analysis.
Table 2: Relative injury risk associated with the use of various psychoactive substances by motorists.

<table>
<thead>
<tr>
<th>Psychoactive substances</th>
<th>Cases (n=110)</th>
<th>Controls (n=816)</th>
<th>Odds ratios</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No substance</td>
<td>56.4%</td>
<td>85.7%</td>
<td>1.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Cannabis</td>
<td>0.9%</td>
<td>4.8%</td>
<td>0.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>0.0%</td>
<td>1.0%</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Cocaine</td>
<td>0.0%</td>
<td>0.3%</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Opiates</td>
<td>3.6%</td>
<td>2.1%</td>
<td>2.6</td>
<td>(p &lt; 0.10)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>2.7%</td>
<td>0.9%</td>
<td>4.4</td>
<td>(p &lt; 0.05)</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>0.0%</td>
<td>0.5%</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Drug combinations</td>
<td>10.0%</td>
<td>1.7%</td>
<td>8.8</td>
<td>(p &lt; 0.01)</td>
</tr>
<tr>
<td>BAC 0.2-0.5 g/L</td>
<td>0.9%</td>
<td>1.5%</td>
<td>0.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>BAC 0.5-0.8 g/L</td>
<td>1.8%</td>
<td>0.5%</td>
<td>6.1</td>
<td>(p &lt; 0.05)</td>
</tr>
<tr>
<td>BAC 0.8-1.3 g/L</td>
<td>1.8%</td>
<td>0.6%</td>
<td>4.5</td>
<td>(p &lt; 0.10)</td>
</tr>
<tr>
<td>BAC &gt; 1.3 g/L</td>
<td>10.0%</td>
<td>0.3%</td>
<td>48.0</td>
<td>(p &lt; 0.01)</td>
</tr>
<tr>
<td>Alcohol+drugs</td>
<td>11.8%</td>
<td>&lt;0.1%</td>
<td>458.2</td>
<td>(p &lt; 0.01)</td>
</tr>
</tbody>
</table>

Increased risk of road trauma (\(p <0.05\)) was associated with single use of benzodiazepines or alcohol, when resulting in a BAC between 0.5 and 1.3 g/L. High relative risk factors were associated with combinations of several drugs and with BACs over 1.3 g/L. An extremely high risk factor was associated with (generally) high BACs in combination with illicit drug use. No enhanced risk was determined for single use of alcohol, resulting in a BAC between 0.2 and 0.5 g/L, and for single use of cannabis, amphetamines, cocaine, tricyclic antidepressants, or opiates. Only for single opiate use, an odds ratio of more than 1 was found; this result, however, was not statistically significant (\(p < 0.10\)). It should be noted that 76% of all motorists in the control group who had been tested positive for cannabis, had used no other psychoactive substances. For cocaine and amphetamine users, however, it was the other way around; 69% and 62% of them, respectively, had also used one or more other illicit drugs.

Figure 1: Psychoactive substance use by motorists in weekend nights, in the Netherlands (1997/98) and the Tilburg police district (2000/01).
When comparing the Tilburg control group data for weekend nights only, with similar nationwide data of 1997/1998 (4,12), it is obvious that illicit drug use in the Tilburg control group is much higher (Figure 1). This may indicate that the use of illicit drugs by Dutch motorists is rapidly growing. Although it is not certain that illicit drug use in the Tilburg police district is representative of the Netherlands, in 1997/98 there was no difference between the Netherlands and the southern region that the Tilburg district is part of.

Discussion
An important source of potential bias was non-response, especially in the control sample. Although no indications of a strong bias have been found, future data collection should aim at a further reduction of non-response. In the first 12 roadside sessions following the feasibility study (until mid-April 2002), non-response was indeed reduced: only 72 out of the 739 motorists who where selected for interviewing and sampling of a body fluid, did not deliver a specimen. A major factor in this reduction was the increased experience of the roadside research team.

Another source of potential bias was the fact that, for psychoactive substances other than alcohol, the detection window in urine is wider than in blood. This is especially the case for cannabis. In the control sample, 85% of specimens consisted of urine, against no more than 39% in the case group. Further analysis of the control sample, however, suggests that the actual bias is limited: 4.8% of the urine specimens were found to be positive for cannabis, against 4.0% of the blood specimens.

Between the early 1970s and 2000, drink-driving in the Netherlands decreased considerably. In weekend nights, the share of motorists with a BAC over 0.5 g/L, dropped from 16% to 4.5%. But despite this, and the probable increase of drug-driving in recent years, alcohol still seems to be the predominant risk factor in road traffic. This might be due to a disproportionate small decrease of hardcore drinking drivers, part of whom are now combining high BACs with illicit drug use.

References
5. Belgian Toxicology and Trauma Research Group. A scientific study on the presence of alcohol, medicines and illegal drugs in drivers who were victim of a traffic accident and the relationship between these substances and the accidents. Brussels, 1996.