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Relationship Between THC Concentration in Blood and Impairment in Apprehended Drivers

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Objective. *The most important psychoactive ingredient in cannabis, Δ (9)-tetrahydrocannabinol (THC) is one of the most frequently detected substances in blood samples from suspected impaired drivers in Norway. There is growing concern over possible links between the use of cannabis and increased risk of motor-vehicle crashs. Experimental studies have provided useful information on the role of THC and dose-effect relations with respect to psychomotor performance. The main purpose of the present study was to investigate whether a physician's judgment on impairment in a real-life setting among suspected drugged drivers, was related to blood THC concentration.*

Methods. *In Norway a police physician performs a clinical test for impairment (CTI) shortly after apprehension. The Norwegian Institute of Public Health analyze blood samples from all drivers suspected of driving under the influence of non-alcoholic drugs. In the present study 589 samples from approximately 30,000 cases of suspected drug impaired driving from the period 1997–99, contained THC as the only drug. In 456 of these cases a conclusion of the CTI was available.*

Results. *230 (54%) drivers were considered not impaired and 226 (46%) impaired. Impaired drivers had higher blood THC concentration than the drivers who were judged as not impaired (median; 2.5 ng/mL (range; 0.3–45.3 ng/mL) vs 1.9 ng/mL (range; 0.32–24.8 ng/mL), (p < 0.05). Furthermore, drivers with blood THC concentrations above 3 ng/mL had an increased risk for being judged impaired compared to drivers with lower concentration ranges.*

Conclusion. *The relationship between the concentration of THC in blood and risk of being assessed impaired found in this cross-sectional study of suspected drugged drivers, supports findings from previous experimental studies of concentration related effects of THC on psychomotor performance and driving skills.*

Keywords   Cannabis; Psychomotor Impairment; Drugged Driving; THC Concentration

The use of cannabis has increased considerably during the past decade in the Western world (Christophersen et al., 1990; Gmel 2002; Hall et al., 2001) and many countries are investigating the therapeutic potential of cannabis. Although the cannabis plant contains over 400 chemical compounds, it is accepted that delta (9)-tetrahydrocannabinol (THC) is primarily responsible for the psychoactive properties of the plant.

Experimental studies have repeatedly demonstrated the THC effects on cognitive functions and psychomotor skills; i.e., THC impairs learning and the acquisition of information, short-term or working memory, divided and sustained attention, reaction time, tracking, and motor control (Chait and Pierri, 1992; Kurzthaler et al., 1999; Leirer et al., 1989). In general, good correlation between THC concentration and various impairing effects have been demonstrated, and these effects of THC on cognitive and psychomotor functions can be related to driving

performance (Berghaus et al., 1998a; Berghaus et al., 1998b; Robbe, 1994). Therefore, based on the concentration-effect relationship for psychomotor performance effects of the THC, it could be suggested to introduce "legal concentration limits" for blood THC concentration as it has been implemented for alcohol in many countries.

Experimental research has, however, some disadvantages. Due to ethical considerations it is not possible to administer high enough cannabis doses to obtain the THC concentrations often found in real-life settings. The studies will most often be single dose experiments. The subjects included in experimental research are less often experienced users, excluding possible tolerance as a part of the studies. It could thus be argued that findings from such experimental studies would have limited relevance for real-life impairment of cannabis in experienced users, and that concentration-effect relationship for THC not would be clear in a population with mixed cannabis experience.

THC is among the drugs most frequently detected in blood samples from suspected drugged drivers (Christophersen et al., 1990; Waller et al., 1997). In Norway a police physician performs a clinical test for impairment (CTI), in conjunction with

the collection of blood samples, shortly after apprehension of drivers suspected of driving under the influence of non-alcoholic drugs (Bramness et al., 2002). We wanted to address the question raised above as to whether a concentration effect relationship would be found for THC in a population using cannabis in a potentially illegal setting (DUI) by comparing the physician's conclusion to the concentration of THC in blood at the CTI.

METHODS

Materials

The Division of Forensic Toxicology and Drug Abuse (DFTDA) at the Norwegian Institute of Public Health analyzed blood samples from all drivers suspected of drugged driving in Norway. All the present data were taken from an existing database at the DFTDA and were handled anonymously by the researchers. This database contained results from all cases of suspected driving under the influence of alcohol and non-alcohol drugs, counting approximately 30,000 cases in the period 1997–1999. The database was searched for positive THC-blood cases. There were 589 samples that contained only cannabis with no other drugs or alcohol above limits of detection. Of these cases, 133 cases were excluded because the examining physician did not present a conclusion after having performed CTI. We had no information on reasons for not performing CTI. The remaining 456 cases constituted the material of this study.

Analytical Methods

All blood samples received at DFTDA were routinely screened for alcohols and common drugs of abuse (amphetamine, benzodiazepines, cannabis, cocaine, and opiates) by immunological methods (Christophersen et al., 1990). The immunological method used was Enzyme Multiplied Immunoassay Test (EMIT II Plus) produced by Dade Behring Diagnostica (Syva, USA) analyses of extracts of haemolysed full blood that has proved to be rapid and simple screening method for cannabinoids (Gjerde et al., 1990; Gjerde, 1991; Peel & Perrigo, 1981). The THC concentration was subsequently determined by a modification of a GC-MS-method described previously (Christophersen, 1986; Gustafson et al., 2003). To achieve adequate sensitivity, lengthy and labor-intensive liquid-extraction procedures were used with hexane and without pH adjustment. After evaporation of the organic phase, THC was trimethyl silylated (TMS) with bistrimethylsilyl-trifluoroacetamide (BSTFA): acetonitrile (2:1) making the THC/TMS derivative. Gas chromatography/mass spectrometry (GC/MS) in SIM mode was eventually used for the analyses (Christophersen, 1986; Gustafson et al., 2003). As a forensic laboratory an administrative cut-off value is set clearly above the lowest limit of quantification (LLOQ). The LLOQ was calculated by the mean of noise adding 10 standard deviation to this mean. The cut-off value for the GC/MS analysis in whole blood for THC was 1 ng/ml. The interday coefficient of variation at 1 ng/ml was 10%. The cut-off value for the immunological screening analyses in whole blood for cannabinoids was 10 ng/ml.

Clinical Test for Impairment (CTI)

In all the cases of suspected drugged driving, a police physician performed CTI shortly after the apprehension of the drivers. Norwegian drivers suspected of driving under the influence of alcohol or non-alcoholic drugs are not at liberty to refuse blood sampling. Due to practicalities (gaining permission, finding a physician) the time between apprehension and completing the CTI with collection of blood samples was about two hours. Only in some police districts there are specially assigned doctor physicians on call. Since each Norwegian physician will perform only a few CTIs each in their life-time, and the fact that we have only examined between one and two percent of the total number of cases, it makes unlikely that one physician has performed more than one CTI in the present material.

The CTI in Norway consist of three elements: 1) A short interview in which the suspected driver is asked about drinking habits and drug history, as well as recent use; 2) Twenty-seven observations and tests (including seven tests of alertness, cognitive function and vestibular function, four observations of the eyes, two observations on cardiac action, two observations pertaining signs of intravenous drug abuse, four tests of motor activity/coordination, and eight observations concerning appearance) (Bramness et al., 2002); and 3) An evaluation of other possible reasons for impaired driving (disease, etc). The physician then concludes whether the suspected driver is "not impaired" or "impaired." The conclusion of the CTI is based on the physician's overall impression of the apprehended driver and not on a sumscore of the individual tests included in the CTI. The conclusion was the only variable of CTI included in the present study. Blood sampling was performed in conjunction with CTI. Blood samples were collected in 5 ml Vacutainer containing sodium and heparin as anticoagulants. The CTI report and the blood samples were sent together to DFTDA by express mail. This procedure has been controlled in separate studies as a part of the running quality control of our procedures. Thus it has been demonstrated that no change of THC-concentrations occurs for periods up to one week in whole blood samples stored in the containers which are provided by DFTDA to collect blood.

Data Analysis

Data analyses were performed using *Statistical Package for Social Sciences* (SPSS) version 12.0.1. Differences between two groups were examined using either Pearson's χ^2-test for categorical data, a Student's t-test for continuous variables with a normal distribution, or a Mann-Whitney test for variables without a normal distribution. A binary logistic regression model was applied to determine odds ratios (ORs) and their 95-percent confidence intervals (CI). Levels of significance for all analysis were set to $P < 0.05$ and $P < 0.01$.

RESULTS

Background Variables

Some of the background characteristics of the present material are given in Table I. Women were more often apprehended by the

Table I Background characteristics of the studied population according to gender. Only significant differences are depicted

Characteristic	Male N = 437 (95.8%)	Female N = 19 (4.2%)
The suspected driver		
Age (years) (mean ± SD)[1]	25 ± 7	28 ± 8
BMI (kg/m^2) (mean ± SD)[1]	23 ± 5.7	21 ± 2.4[4]
Regular use of cannabis[2]	170 (39%)	7 (37%)
Signs of i.v. abuse		
Needle marks (%)[2]	119 (27 %)	9 (47 %)
Thrombosis (%)[2]	48 (11 %)	5 (26 %)
The incident		
Accident (number of accidents) (%)[2]	52 (12 %)	7 (37 %)[5]
Type of vehicle (number of private cars) (%)[2]	414 (95 %)	19 (100 %)
Examination and analytical results		
Number of impaired drivers (%)[2]	213 (49 %)	13 (68 %)
Blood Δ^9-THC concentration (ng/mL) (median; range)[3]	2.2 (0.3–45.3)	1.3 (0.3–18.9)[5]

[1]Result based on Student's t-test ($P < 0.01$).
[2]Result based on χ^2-test ($P < 0.05$).
[3]Result based on Mann-Whitney-test ($P < 0.05$).
[4]$P < 0.01$.
[5]$P < 0.05$.

police due to crashes. Further analyses concerning crashes were not performed, because the crash data were considered incomplete. Female drivers had more often signs of i.v. drug abuse. The interrelations between all the other background variables were studied in detail. Drivers of non-private cars were older than the drivers of private cars (mean [SD]) 32 years (±7.7 years) versus 26 years (±6.7 years) ($p < 0.05$, Student's t-test). Drivers apprehended after a car crash less often had signs of i.v. abuse (p < 0.05, χ^2-test). Older drivers more often volunteered information on regular use of cannabis ($p < 0.01$, Student's t-test). Older drivers more often had signs of i.v. abuse ($p < 0.001$, Student's t-test). Lastly, the different signs of i.v. abuse correlated with one another.

Blood THC Concentration
The median blood THC concentration was 2.2 ng/mL with a range from 0.3 to 45.3 ng/mL. Male drivers had higher blood THC concentration than female (2.2 ng/mL [0.3–45.3] vs. 1.3 ng/mL [0.3–18.9], $p < 0.05$, Mann-Whitney test). Those with needle marks had lower blood THC concentration than those without (median 1.6 ng/mL [0.3–19.8] vs. 2.5 ng/mL [0.3–45.0], p < 0.01, Mann-Whitney test).

Impairment
Of the 456 apprehended drivers 230 (54 percent) were judged as impaired by the police physician. Drivers apprehended after reported crashes were less often impaired than drivers apprehended for other reasons ($p < 0.01$, χ^2-test). Drivers who had signs of i.v. abuse were more often judged as impaired ($p < 0.01$, χ^2-test).

These relationships between background variables and impairment were tested in multivariate analysis to check if these relationships could be explained by differences in THC concentrations in the different groups, even if these differences did not emerge in the bivariate analysis between drug concentration and background variables. The bivariate relationships (between impairment, crash, and signs of i.v. abuse) withstood adjustment for blood THC concentration.

Regular Versus Occasional Use
Those drivers who claimed to be regular users of cannabis were less often judged as impaired (32% vs 55%, $p < 0.01$, χ^2-test), but there was no difference in THC concentration between regular users and non-regular users. In a multiple regression model the impact of regular use withstood adjustment for THC concentration (OR regular user = 1, OR occasional users = 1.8 95% CI [1.2–2.7], $p < 0.01$).

Drug Concentration and Impairment
The drivers who were judged as impaired had higher blood THC concentration than the drivers who were judged as not impaired (median; 2.5 ng/mL [0.3–45.3 ng/mL] vs 1.9 ng/mL [0.32–24.8 ng/mL], ($p < 0.05$, Mann-Whitney test). We grouped THC concentrations in six concentration intervals. The percentage of drivers judged impaired increased from 38 percent in the lowest concentration group to 57 percent in the highest (Figure 1). In a binary logistic regression model (Table II) the odds ratio (OR) for being judged impaired increased with increased drug concentrations from 2.9 ng/ml. This relationship did not withstand adjustment for regular use, but was strengthened by adjustment for signs of i.v. abuse. A fourth step involving adjustment for both regular use, signs of i.v. abuse, and gender gave a rising OR for being determined impaired from blood THC concentrations above 2.9 ng/ml.

DISCUSSION

In the present study we found a positive relationship between the concentration of THC in blood and risk of being judged
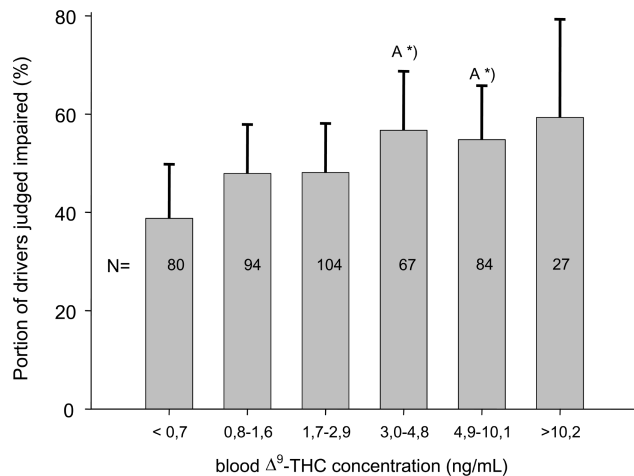
Figure 1 THC-concentrations were grouped in six different concentration intervals. The percentage of drivers judged impaired increases from 37 percent in the lowest concentration group to 57 percent in the highest. The groups of 3.0–4.8 ng/ml and 4.9–10.1 ng/ml were significantly more often judged impaired than the lowest concentration group (<0.7 ng/ml), (p < 0.05, Pearson's χ^2).

impaired by a police physician after suspected drugged driving. Although this relationship is not so obvious as in the case it is for alcohol or benzodiazepines (Bramness et al., 2002), it was significant. We found that the OR for being judged as impaired was increased in the groups with elevated blood THC concentration. This increased OR withstood adjustment for background variables as gender, needle marks, and regularity of use. THC has previously been shown in a series of experimental laboratory studies to impair psychomotor function in a concentration related fashion (Berghaus et al., 1998a). These have generally demonstrated that THC in doses up to 300 μg/kg causes a dose dependent reduction in performance. The highest THC dose resulted in impairing comparable to the impairing effects of an alcohol dose producing a BAC $\geq$ 0.05 g/dl (Berghaus et al., 1998a; Berghaus et al., 1998b; Ramaekers et al., 2000; Robbe 1994).

In the present study the median concentration of THC in the impaired drivers was 2.5 ng/ml, significantly higher than those not judged as impaired. Previous studies demonstrated that recent exposure and possible measurable impairment have been linked to plasma THC concentrations in excess of 2–3 ng/ml Huestis et al., 1992; Mason & McBay 1984), or 3–5 ng/ml (Tzambazis & Stough, 2002). The THC concentration

in hemolyzed whole blood is approximately one-half the concentration of the plasma THC concentration and these concentrations would thus correspond to 1.0–1.5 and 1.5–2.5 ng/ml in whole blood (Mason & McBay 1984). Gjerde and Kinn suggested that 1.6 ng/ml THC in whole blood may indicate possible impairment (Gjerde & Kinn, 1991). Krüger and Berghaus, however, estimated from experimental studies the impairment accompanying plasma THC concentrations of 11 ng/ml or 6 ng/ml blood to be roughly equivalent to the impairment accompanying a blood alcohol concentration of 0.073 g/dl (Krüger & Berghaus, 1995).

Drivers who claimed to be using cannabis on a regular basis were less often judged as impaired despite no difference in THC concentration between regular users and non-regular users. This may support other studies that report that experienced users develop some degree of tolerance to the acute effects of THC (Howlett et al., 2004). Blood THC concentration is dependent on mode of intake, as well as dose. The meta-analysis by Berghaus et al. indicates that the performance impairment after cannabis intake was highest during the first hour after smoking and between 1–2 hours after oral intake and declined after 3–4 hours (Berghaus et al., 1998a; Berghaus et al., 1998b; Kurzthaler et al., 1999). Experimental studies limit themselves to assessing the acute effects of THC on performance, not addressing the question of tolerance in the experienced user (Sexton et al., 2000; Smiley et al., 1981). In the present study, only 30 percent of the drivers volunteered information on current cannabis intake, indicating that the information given by drivers on other issues like drug experience were also unreliable. As a result, we cannot fully investigate if cannabis users adapt to the acute effects of the drug as a result of tolerance. The effects of THC in novel users versus experienced users are currently not known in sufficient detail, but the present study may suggest some degree of tolerance.

There are several limitations to the present study. Previous studies have indicated that instruments like the CTI may have a low sensitivity for detection of driving performance impairment (Kuitunen, 1994). One study failed to find a relation between THC concentration and results of such a test (Reeve et al., 1983). Introducing alternative tests like looking for the presence of head jerks might improve the sensitivity of the CTI to THC induced impairment. A time lag between intake of cannabis and blood sampling could obscure the relationship between blood THC concentration and clinical outcome. Due to inverse hysteresis

Table II Odds ratios (OR) and 95 percent confidence intervals (CI) for being determined "impaired" at six different levels of blood Δ^9-THC concentrations

	Blood Δ^9-THC concentrations (ng/mL) and OR (95% CI)					
	<0.7[1]	0.8–1.6	1.7–2.9	3.0–4.8	4.9–10.1	>10.2
Drug concentration unadjusted	1	1.5 (0.8–2.7)	1.5 (0.8–2.7)	2.1 (1.1–4.0)[2]	1.9 (1.1–3.6)[2]	2.3 (0.9–5.6)
Drug concentration adjusted for regular use	1	1.5 (0.8–2.8)	1.3 (0.7–2.4)	1.8 (0.9–3.7)	1.8 (0.9–3.4)	2.5 (1.0–6.6)
Drug concentration adjusted for the presence of needle marks	1	1.6 (0.8–3.0)	1.6 (0.9–3.0)	2.6 (1.3–5.3)[3]	2.6 (1.3–5.1)[3]	2.9 (1.2–7.3)[2]
Drug concentration adjusted for gender, needle marks and regular use	1	1.7 (0.9–3.2)	1.6 (0.8–3.0)	2.4 (1.1–5.0)[2]	2.5 (1.3–5.0)[2]	3.2 (1.2–8.7)[2]

[1]reference category.
[2]$P < 0.05$.
[3]$P < 0.01$.

even low blood THC concentrations may be seen as impaired. Furthermore, it is difficult to be sure of the external validity of the CTI (what would be the gold-standard to test external validity?). But the internal validity has been studied in several papers from our department (Bachs et al., 2003; Bramness et al., 2002; Bramness et al., 2004). Likewise, we do not know the reliability of the CTI. As each doctor performs only some tests during their career they have little experience in judging impairment. All these limitations could, however, have reduced any concentration effect relationship. But neither the low sensitivity of the CTI, individual variation in drug sensitivity, nor the low reliability or inter-examiner variation obscured the relationship between blood THC concentration and CTI performance. Hence, our findings must be viewed as a robust result and indicate that THC has impairing effects also in a real-life setting as described for benzodiazepines by our group (Bramness et al., 2002).

Culpability studies estimate the odds ratios for being responsible in fatal or injurious traffic accidents. Such studies have been performed for drivers with cannabis alone or in combination with alcohol in their blood samples. Many studies have used THC-acid as a measurement, and have failed to demonstrate an increased culpability risk (Drummer, 1994; Hunter et al., 1998; Movig et al., 2004; Terhune et al., 1992; Terhune & Fell, 1982). This is not surprising since THC-acid is an inactive metabolite of THC. Drummer et al. demonstrated an elevated risk for THC blood concentration between 1 and 100 ng/mL, and an even more elevated risk at blood concentrations between 5 and 100 ng/mL (Drummer, 1994; Drummer et al., 2003; 2004). A recently published population-based case-control study also indicated that habitual use of cannabis was strongly associated with car crash injury (Blows et al., 2005). The paucity of studies addressing the relationship between blood THC concentration and impairment in real-life settings makes the present results of some interest, as we replicate the findings of experimental research in a diverse population most likely having variable cannabis experience, as well as variation in dose ingested and in time between intake and testing.

In conclusion, a positive relationship between the concentration of THC in blood and the risk of being assessed as impaired, observed in this study, is compatible with the assumption of concentration dependent negative effect of cannabis upon driving performance previously indicated by experimental and accident culpability studies.

ACKNOWLEDGMENTS

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