Comparison of the prevalence of alcohol, cannabis and other drugs between 900 injured drivers and 900 control subjects: results of a French collaborative study

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Abstract

A collaborative case-control study was conducted in France in order to determine the prevalence of alcohol, cannabinoids, opiates, cocaine metabolites, amphetamines and therapeutic psychoactive drugs in blood samples from drivers injured in road accidents and to compare these values with those of a control population. Recruitment was performed in emergency departments of six university or general hospitals and comprised 900 drivers involved in a non-fatal accident and 900 patients (controls) who attended the same emergency units for a non-traumatic reason. Drivers and controls were matched by sex and age. Alcohol was determined by flame ionization–gas chromatography, drugs of abuse (DOA) by gas chromatography–mass spectrometry with the same analytical procedures in the six laboratories, and medicines by high performance liquid chromatography with diode array detection.

Blood alcohol concentration exceeding 0.5 g/l (i.e. the legal French threshold) was found in 26% of drivers and 9% of controls. In the 18–27 years age range, alcohol was the only toxic found in blood samples of 17% drivers and 5% controls, leading to an odds-ratio (OR) of 3.8. A significant relationship was found between alcohol blood concentrations and OR values. All age groups confounded, the main active substance of cannabis, Δ^9 tetrahydrocannabinol (THC), was found in 10% of drivers and 5% of controls. In the less than 27 years old, THC (>1 ng/ml) was detected alone in the blood of 15.3% drivers and of 6.7% controls, giving OR = 2.5, whereas there was no link between THC blood concentrations and OR value. THC was found alone in 60% of cases and associated with alcohol in 32%, with OR = 4.6 between drivers and controls for this association. The difference in morphine prevalence between drivers (2.7%) and controls (0.03%) was highly significant ($P < 0.001$), with OR = 8.2. The number of positive cases for amphetamines and cocaine metabolites was too low for reaching any interpretation. The most frequently observed psychoactive therapeutic drugs were by far benzodiazepines, that were found alone in 9.4% of drivers and 5.8% of controls, which led to OR = 1.7 ($P < 0.01$).

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This study demonstrates a higher prevalence of opiates, alcohol, cannabinoids and the combination of these last two compounds in blood samples from drivers involved in road accidents than in those from controls, which suggests a causal role for these compounds in road crashes.

1. Introduction

Most drugs that affect the central nervous system may have the potential to impair driving ability. Alcohol, drugs of abuse (DOA: opiates, amphetamines, cocaine and cannabis) and prescribed psychoactive drugs are potentially concerned. For many years, attention has primarily focused on alcohol and most countries have established legal limits for blood alcohol concentration during driving. However, during the last years drugs other than alcohol have attracted increasing attention, due to a dramatic increase of use, particularly for cannabis which is by far the most consumed DOA in France as well as in many other countries. Research on the impairing effects of these psychoactive compounds has included several approaches [1]. Some studies have evaluated the effects of drugs on cognitive and/or psycho-motor tasks after controlled administration [2–4]. Others have investigated drugs effects in situations mimicking real driving such as driving simulators [5,6] and closed or open-road driving trials [7]. All these studies highlighted the increased risk of road crashes for drivers under the influence of these drugs, but did not provide the magnitude of the problem nor quantify accident risk. It is the reason why a very large number of epidemiological studies have been performed in many countries. Most of them have been focused on the determination of the prevalence of drivers involved in fatal or non-fatal motor vehicle accidents while being under the influence of drugs. However, the value of a number of these studies in measuring how frequently do people drive under the influence of drugs is weak, because they did not use appropriate analytical procedures [8], i.e. determination of the active forms of the main DOAs in blood, using sensitive and specific analytical procedures, with appropriate cut-off values. In France, for example recent studies have shown that the potentially impairing compounds most frequently found in blood samples from drivers involved in fatal and non-fatal accidents are respectively alcohol, cannabinoids and benzodiazepines [9–11]. This finding has also been observed in many other countries. When they use appropriate methodology, these observational studies are of interest because their results can lead the concerned countries to undertake appropriate prevention actions. However, a better knowledge of the role played by drugs in the occurrence of accidents is afforded when drivers are compared to a control group, but such case-control studies have seldom been performed. An Australian case-control study performed in injured drivers [12] revealed a significant relationship between alcohol, benzodiazepines and responsibility for the car crash, but this relation was not significant for cannabinoids and stimulants. However, the cut-off used in blood for cannabinoids was 40 ng/ml, which is by far too high [13], since THC blood concentrations decline rapidly down to a few ng/ml while impairing effects are still present [14].

The present article reports the results of a French multi-centre study whose aim was to compare the prevalence of alcohol, drugs of abuse (cannabinoids, amphetamines, cocaine metabolites and opiates) and psychoactive thera-peutic drugs in blood in two groups: one of 900 injured drivers and other of 900 age- and sex-matched controls.

2. Materials and methods

The emergency care units (ECU) and toxicology labora-tories from six French university or general hospitals parti-cipated in the study: Grenoble, Le Havre, Limoges, Lyon, Poitiers, and Strasbourg. Blood was used as the biological matrix to screen for alcohol, cannabinoids, opiates, cocaine metabolites, amphetamines and psychoactive therapeutic drugs. The samples were collected from June 2000 to September 2001.

2.1. Populations

Nine hundred drivers (150 per centre) involved in a non-fatal road accident and admitted in the emergency units were included in "drivers group". In order to part the recruitment of cases and controls over every month of the year and every day of the week, from the first of each month, each centre recruited a maximum of 13 drivers. The drivers who received one of the studied drugs such as morphine, benzodiazepines or barbiturates during their transportation to the ECU were excluded. Only car drivers were included in this study.

The control group was comprised of 900 patients having a driving license and who attended for any non-traumatic reason the same emergency units as the cases. The patients who received one of the studied drugs and those admitted for voluntary or accidental intoxication (including alcohol) were excluded. "Drivers" and "patients" were matched by sex and age (with a tolerance of ±1 year).

Initially, 933 drivers and 933 patients were recruited: 33 drivers and 33 patients were excluded because the volume of

blood sampled was not sufficient for screening all the compounds of interest.

2.2. Biological samples and storage

Blood samples were collected in 10 ml glass tubes with lithium heparinate and kept at 4 °C for analysis within 48 h or otherwise frozen at −20 °C. The time between the road crash and blood sample collection varied across drivers, with an average of 1.8 h, and a standard deviation of 0.9 h.

Additionally, urine samples were collected in 50 ml plastic containers with plastic screw caps.

When urine sampling was not possible, sweat was collected on the patient's forehead according to the method proposed by Kintz et al. [15]. Urine or sweat sampling was mainly necessary for opiate positive cases, to discriminate heroin administration from other opiates, using the presence of 6-acetylmorphine as a heroin intake positive marker.

2.3. Screened compounds and methods

The following compounds were screened in blood:

- Ethanol by flame ionization–gas chromatography.
- *Cannabinoids*: Δ^9 tetrahydrocannabinol (THC), 11-hydroxy-Δ^9 tetrahydrocannabinol (11-OH-THC) and 11 nor-9-carboxy-Δ^9 tetrahydrocannabinol (THC-COOH).
- *Amphetamines*: amphetamine, methamphetamine, methylenedioxyamphetamine (MDA), methylenedioxymethamphetamine (MDMA).
- *Opiates*: morphine, codeine, codethyline.
- *Cocaine*: benzoylecgonine, ecgonine methylester, cocaethylene, anhydroecgonine.

Table 1
Age distribution in the two groups

Age (years)	Drivers	Controls
18–22	182	176
23–26	139	134
27–30	130	124
31–39	149	151
40–49	137	149
>50	163	166

- *Other psychoactive drugs*: barbiturates, benzodiazepines, antidepressants.

Drugs of abuse were analysed in the six laboratories with the same procedures using gas chromatography–mass spectrometric [16–18], as recommended by the French Society of Analytical Toxicology.

Psychoactive therapeutic drugs were determined by high performance liquid chromatography with diode array detection with different in-house methods.

2.4. Statistical analysis

The potential differences in prevalence of drugs and odds-ratios (OR) were determined by Fisher's Exact Test using GraphPad Instat® software running on an IBM-compatible microcomputer.

3. Results and discussion

The distribution according to age is presented in Table 1. Females represented 25.7% of the drivers.
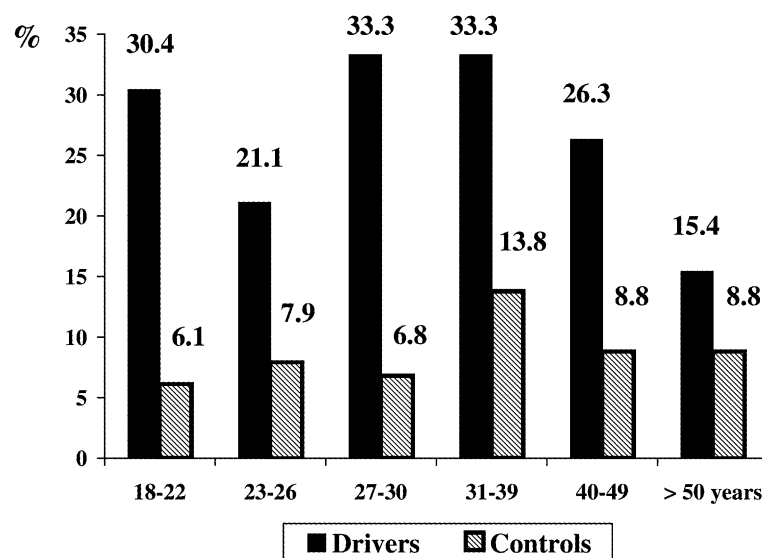

Fig. 1. Percentages of drivers and controls testing positive for ethanol, according to age.
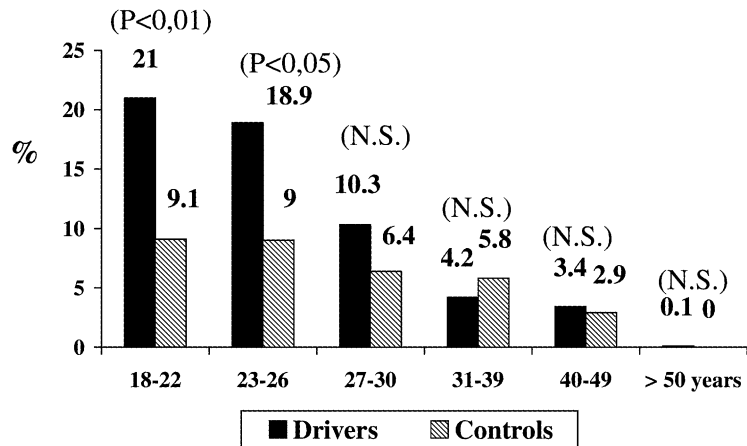
Fig. 2. Percentages of drivers and controls testing positive for THC, according to age. The results of statistical comparisons are included in brackets.

Table 2
Prevalence of the mainly found compounds and combinations of compounds in blood of drivers and controls

Drugs (positivity thresholds)	Positive (%)		Odds-ratios (95% confidence interval)
	Drivers	Controls	
Alcohol only (>0.5 g/l)[a]	17.0	5.0	3.8 (2.1–6.8)
THC only (>1 ng/ml)[a]	14.1	6.7	2.5 (1.5–4.2)
Alcohol + THC[a]	9.5	2.2	4.6 (2.0–10.7)
Morphine (>20 ng/ml)[b]	2.7	0.3	8.2 (2.5–27.3)
Benzodiazepines only	9.4	5.8	1.7 (1.2–2.4)

[a] Less than 27 years old.
[b] All ages included.

3.1. Alcohol

In accordance with French laws, subjects were considered to be positive when alcohol blood concentration exceeded 0.5 g/l. Under these conditions, 26% of all drivers and 9% of all controls were positive. The prevalence of alcohol use in drivers and in controls according to age is presented in Fig. 1: the difference between drivers and patients was highly significant ($P < 0.001$).

Road accidents are in France the first cause of death in the 18–27 years age range. In this population, alcohol was the only toxic found in blood of 55 drivers (17%) and 16 patients (5%) (Table 2), leading to an odds-ratio of 3.8. Table 3 shows that when blood alcohol concentrations increased, so did the differences between the prevalence in drivers and controls. Such values are not surprising and confirm previously published data [12].

3.2. Cannabinoids

In accordance with French laws [19], subjects were considered to be positive when THC blood concentration exceeded 1 ng/ml. Accordingly, when only THC–COOH was found, subjects were considered to be negative since the presence of this compound can only attest for a previous consumption of cannabis but not for impairment at the time of blood sampling. Under these conditions, all age groups pooled, 10% of drivers and 5% of controls were positive for cannabis. The prevalence of THC in drivers and in controls according to age is presented in Fig. 2: the difference between the two groups was highly significant in 18–22 ($P < 0.01$) and 23–26 ($P < 0.05$) years age ranges.

In the less than 27 years age range, THC (above 1 ng/ml) was found alone in the blood of 49 drivers (15.3%) and 21

Table 3
Prevalence of alcohol (alone) in blood of drivers and controls, according to concentrations

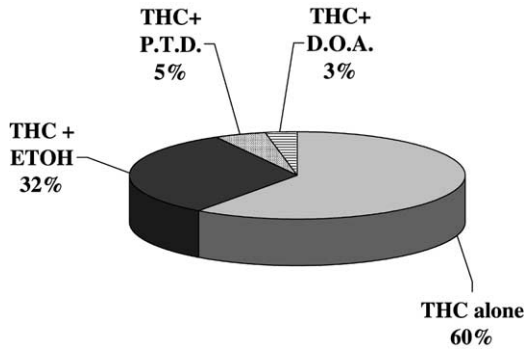| Alcohol concentration (g/l)	Positive (%)		Odds-ratios (95% confidence interval)
	Drivers	Controls	
0.50–0.79	2.4	1.1	2.2 (1.1–4.7)
0.80–1.19	2.9	1.1	2.7 (1.3–5.5)
1.20–1.99	7.1	2.1	3.6 (2.1–6.0)
≥2.0	9.8	1.7	6.4 (3.7–11.1)

Fig. 3. Combinations of THC with other compounds. ETOH: ethanol; P.T.D.: psychoactive therapeutic drugs; D.O.A.: other drugs of abuse.

patients (6.7%; Table 2), giving OR = 2.5. When adding to these cases those where THC blood concentration was between 0.2 ng/ml (i.e. the analytical threshold) and 1 ng/ml (i.e. the French legal positivity threshold [19]), no significant difference in odds-ratios was observed between the studied groups (drivers and control) with THC concentrations under 2 ng/ml and the group with concentrations above 2 ng/ml, since the odds-ratios were 2.5 and 2.7, respectively. We were not surprised by this finding because several previous studies have shown that THC concentrations in blood were not directly related to a specific degree of driving impairment. Indeed, peak THC blood levels are achieved within a few minutes of the initiation of smoking and rapidly decline, but peak clinical effects are delayed for some 20–30 min, as the drug distributes from the blood into the brain and other tissues [1,14,20,21].

As illustrated in Fig. 3, among those positive for cannabis (whether drivers or controls), THC was alone in 60% and associated to alcohol in 32%, with OR = 4.6 between drivers and patients (prevalence of 9.5 and 2.2%, respectively).

3.3. Other drugs

Subjects were considered positive for opiates when morphine concentration in blood exceeded 20 ng/ml. The difference in morphine prevalence between drivers (2.7%) and patients (0.03%) was highly significant ($P < 0.001$), with OR = 8.2.

In accordance with the recent French law, the positivity threshold for blood concentration of amphetamine and related compounds was set at 50 ng/ml, whatever the compound. A very few number of positive cases were found in drivers ($n = 6$) as well as in controls ($n = 3$). In the six positive drivers, the compound found was MDMA (associated with MDA which is its main metabolite), with concentrations ranging from 50 to 314 ng/ml.

Cocaine metabolites were present in only one driver (benzoylecgonine 81 ng/ml; ecgonine methylester 9 ng/ml), associated with alcohol (0.48 g/l), morphine (20 ng/ml) and benzodiazepines (bromazepam 310 ng/ml; nordiazepam 1300 ng/ml) and in one control (benzoylecgonine 45 ng/ml; ecgonine methylester 12 ng/ml) associated with alcohol (1.1 g/l) and MDMA (52 ng/ml).

Psychoactive therapeutic drugs were found alone in the blood of 142 drivers (15.8%) and of 107 controls (11.9%) (significant difference, $P < 0.05$). As illustrated in Fig. 4, the prevalence of psychoactive medicines when present alone in blood increased with age, in drivers as well as in controls. Table 4 shows that the most frequently observed compounds in the two groups were by far benzodiazepines, for which the prevalence of each type is indicated in Table 5. Moreover, benzodiazepines were found alone in 9.4% of drivers and 5.8% of patients, which led to OR = 1.7 ($P < 0.01$). These results, which suggest an increased risk
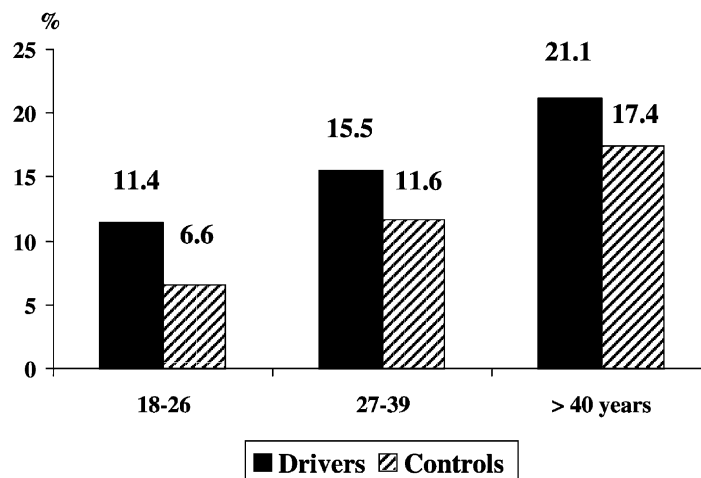

Fig. 4. Percentages of drivers and controls testing positive for psychoactive therapeutic drugs, according to age.

Table 4
Prevalence of psychoactive therapeutic drugs (alone or in combination) in blood of drivers and controls

Drugs	Positive (%)	
	Drivers ($n = 900$)	Controls ($n = 900$)
Benzodiazepines[a]	14	12.6
Antidepressants	1.8	1.1
NSAIDs	1.4	2.2
Antiepileptics[b]	1.1	0.7
Hypnotics	0.9	0.3
Antitussive	0.7	0.9
Others	2.8	2.4

[a] Hypnotic benzodiazepines excluded.
[b] Benzodiazepines excluded.

Table 5
Percentages of injured drivers and controls testing positive for each type of benzodiazepine[a]

Type of benzodiazepine	Positive (%)	
	Drivers ($n = 900$)	Controls ($n = 900$)
Nordiazepam	4.6	4.0
Bromazepam	3.0	2.6
Oxazepam	2.4	1.8
Diazepam	1.1	1.5
Tetrazepam	0.7	0.8
Clobazam	0.6	0.5
Lorazepam	0.4	0.4
Midazolam	0.4	0.2
Chlordiazepoxide	0.3	0
Alprazolam	0.2	0.5
Nitrazepam	0.2	0.1
Estazolam	0	0.1
Clonazepam	0	0.1

[a] In many cases, drivers tested positive for more than one benzodiazepine.

of traffic accidents with the use of benzodiazepines, are consistent with previous published French data [22].

4. Conclusion

This study confirms the high prevalence of the use and/or abuse of psychoactive compounds in the French population [23,24]. This is particularly true for cannabis in the young population. Furthermore, our results demonstrate a higher prevalence of alcohol, cannabinoids and the combination of these two compounds in blood samples from drivers involved in road accidents than in those from controls and consequently suggests a causal role for these compounds in road crashes. These findings provide additional arguments

for documenting the impairing effects of such compounds on the ability to drive a car, with respect to studies performed on driving simulators or even in ''realistic'' situations on closed or open-roads.

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