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Prevalence of Drugs of Abuse in Urine of Drivers Involved in Road Accidents in France: A Collaborative Study*

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ABSTRACT: This collaborative, anonymous, case-control study was intended to determine the prevalence of opiates, cocaine metabolites, cannabinoids and amphetamines in the urine of drivers injured in road accidents and to compare these values with those of non-accident subjects (''patients'') in France. Recruitment was performed nationwide in the emergency departments of five hospitals and comprised 296 ''drivers'' aged 18 to 35 and 278 non-traumatic ''patients'' in the same age range. Females represented 28.4% of ''drivers'' and 44.2% of ''patients.'' Screening for drugs in urine was performed by fluorescence polarization immunoassays in each center. Each positive result was verified using gas chromatography-mass spectrometry (GC-MS), in a single laboratory. Statistical analysis comprised single-step logistic regression and simultaneously took account of confounding factors and the final differences in prevalence values between the two populations or different subgroups.

Cannabinoids were found in 13.9% of drivers (16.0% of males and 8.3% of females, $p < 0.05$) and 7.5% of patients (12.3% of males, 1.6% of females, $p < 0.0001$); only in females was this prevalence higher in injured drivers than in patients ($p < 0.05$). Opiates were present in 10.5% of drivers' and 10.4% of patients' urine samples (NS), and were more frequent in urine samples positive for cannabinoids, in drivers ($p < 0.01$) as well as in patients ($p < 0.001$). The prevalence of cocaine metabolites in drivers and patients was 1.0 and 1.1% and that of amphetamines 1.4 and 2.5%, respectively.

No causal relationship between drugs and accidents should be inferred from this retrospective study. Nevertheless, the high prevalence of cannabis and opiate (licit or illicit) use in young people, whether injured drivers or patients, has potential implications for road traffic safety in France. Cocaine and amphetamines did not appear to be a major problem, unlike the experience in other countries.

KEYWORDS: forensic science, forensic toxicology, cannabinoids, opiates, cocaine, amphetamines, urine, driving, substance abuse, traffic accident

The consequences of drug abuse for driving, and above all for road accidents, is a public health concern in all industrialized countries. Numerous studies have addressed this concern, mainly using two different approaches. The first approach examines the effects of controlled administrations of single or increasing doses of a single drug in a small number of volunteers, either on actual driving performance or, more often, on psychomotor skills supposed to be involved in driving and evaluated using simulators (1–3). These experiments sometimes give contradictory results and, in addition, are difficult to extrapolate to the real world. The second approach is based on questionnaires and/or biological sampling of drivers injured or killed in road accidents (4–12), impaired drivers (driving under the influence) (13,14), or targeted subpopulations of drivers such as truck drivers (15). Although such studies provide insight into the prevalence of drug abuse in these respective groups at a given time and place, they cannot assess the exact role that drugs play in road accidents, for methodological reasons. Firstly, most of these studies did not include a control group and therefore did not allow statistical comparisons and risk assessment. Secondly, these studies were conducted at different times using different analytical tools or positivity thresholds, and one cannot therefore establish a correlation between the prevalence of drugs and the rate of road accidents on a geographical basis.

The present work is intended to determine the prevalence of each of the four major classes of illicit drugs (opiates, cocaine, cannabinoids and amphetamines) in the urine of young (18 to 35 years old) drivers injured in road accidents in France, and to compare this prevalence with that of non-accident subjects, by means of a collaborative case-control study.

Materials and Methods

The emergency departments and toxicology laboratories of five university or general hospitals throughout France participated in the study (Fig. 1). Urine was chosen as the medium to screen for cannabinoids, opiates, cocaine metabolites and amphetamines.

Populations—''Drivers'' were 296 drivers of any motorized

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FIG. 1—*Geographical distribution of hospitals involved in the collaborative study.*

vehicle, 18- to 35-year-old males or females, recruited consecutively, night and day in the emergency units of the five hospitals involved, regardless of severity of their injuries, so long as urine could be collected. The comparative group (''patients'') comprised 278 patients of either sex, aged 18 to 35, admitted during the same period to the same emergency units for any non-traumatic reason. Urine was chosen as the screening fluid because, in accordance with French law, as urine sampling is noninvasive and the whole study was strictly anonymous (no data could link a sample to a patient), no consent had to be requested from the subjects and approval by an ethics committee was not necessary. In fact, had the subjects been informed of the aim of the study, most addicts might have refused, leading to bias.

Urine Sampling and Storage—Urine samples were collected in 50 mL plastic containers with plastic screw caps and dispatched to the local toxicology laboratory where they were kept at 4°C for analysis within 48 h, or otherwise were frozen at −20°C.

Analytical Materials and Methods—Drug screening in urine was performed by automated fluorescence polarization immunoassay (FPIA) using an ADX or TDX apparatus (Abbott, France) in each participating laboratory. Three controls (low, medium and high concentrations) were analyzed with each batch of samples so that if values were outside the admissible range a new calibration was done and samples and controls were re-assayed. Positive response thresholds were set at low values, in order to avoid most false-negatives: cannabinoids 50 ng/mL (11 nor 9-carboxy-Δ^9 tetrahydrocannabinol equivalent); opiates 40 ng/mL (morphine equivalent); cocaine and metabolites 50 ng/mL (benzoylecgonine equivalent); amphetamines 200 ng/mL (amphetamine equivalent).

The risk of false-positives was then avoided by verifying all positive results in a single laboratory (Toxicology Laboratory, Préfecture de Police de Paris) using appropriate gas chromatography-mass spectrometry (GC/MS) techniques. An enzymatic hydrolysis with β-glucuronidase was routinely performed before cannabinoid (THC-COOH) analysis. For opiates, urine samples were first assayed before glucuronidase hydrolysis in order to prevent the degradation of 6-monoacetylmorphine (6 MAM, first metabolite of heroin) at acidic pH and high temperature required; then they were hydrolyzed, re-extracted and analyzed for total morphine, codeine, ethylmorphine and pholcodine. No hydrolysis was needed for amphetamines (amphetamine, methamphetamine, MDA, MDEA and MDMA) or for cocaine and its metabolites (benzoylecgonine and ecgonine methylester), which do not undergo glucuronation. After addition of deuterated internal standards, solid-phase extraction procedures were used for each class of drug of abuse (Table 1). Four different capillary GC/MS techniques were performed on a Hewlett-Packard 5890 II gas chromatograph coupled to a Hewlett-Packard 5972 mass spectrometer, operated in the electron-impact, selected-ion monitoring mode (Table 1).

Statistical Analysis—The potential differences in prevalence of drugs, as well as in confounding factors (age, sex, centers) between the two populations or between different subgroups, were simultaneously analyzed by means of single stepwise logistic regressions using maximum likelihood estimate, using BMDP 7.0 software running on an IBM-compatible microcomputer. If their associated probability was less than 10% ($p < 0.1$), confounding factors (such as any differences in sex and age distribution) were first taken into account (included in the model), then final differences in drug prevalence were tested against a probability threshold of 5%. In this way, logistic regression can be regarded as a multidimensional Mantel-Haenszel test that allows the adjustment according to several confounding factors simultaneously. The logistic model allows the computation of the natural logarithm of the odds of an event as a linear combination of independent variables, including confounders, $X_1, X_2 \ldots X_p$:

$$\ln(\text{odds}) = b_0 + b_1X_1 + b_2X_2 + \ldots + b_pX_p \qquad (16)$$

Results

A total of 296 drivers involved in road accidents and 278 patients were recruited in the five centers. Their mean age was 25.5 ± 5.2 and 26.5 ± 5.2 years, respectively ($p < 0.02$). Females represented 28.4% of the ''drivers'' and 44.2% of the ''patients'' ($p = 0.0001$).

The prevalences of drugs in urine of ''drivers'' and ''patients'' are presented, for males and females separately, in Fig. 2. Globally, the respective prevalences for drivers and patients were: 13.8% and 7.6% for cannabinoids; 10.5% and 10.4% for opiates; 1.35% and 2.52% for amphetaminic compounds; 1.10% and 1.08% for cocaine metabolites.

The nature and occurrence of opiates, found by GC/MS in the urine of 30 drivers and of 30 patients, are reported in Table 2; only three urine samples (two drivers' and one patient's) contained 6 MAM, confirming heroin use, while cannabinoids, cocaine metabolites or illicit amphetamines were found in 19 out of 57 samples containing other opiates but not 6 MAM, suggesting an illicit use of opiates.

After adjustment for differences in age and sex distribution, the apparently important difference in cannabis prevalence between drivers and patients was not statistically significant ($p = 0.054$), except in females for whom, after adjustment for a moderate age difference (25.0 years in drivers versus 26.2 years in patients, $p = 0.072$), the prevalence of cannabinoids in drivers' urine was significantly higher than in patients' (8.3% vs. 1.6%; $p = 0.020$), with an OR between 1.1 and 27.8. On the other hand, a higher

TABLE 1—*Main parameters of the gas chromatography-mass spectrometry methods used for the determination of drugs-of-abuse in urine.*

	Opiates	Cocaine and Metabolites	Cannabinoids	Amphetamines
Molecules determined	6 MAM, morphine, codeine ethylmorphine, pholcodine	cocaine, benzoylecgonine, ecgonine-methyl-ester	THC-COOH	amphetamine methamphetamine, MDA MDMA, MDEA
Hydrolysis of conjugates	first none, then with Helix Pomatia juice, at pH 5.3 during 2 h at 56°C	none	with Helix Pomatia juice, at pH 5.3, during 2 h at 56°C	none
Internal standards	nalorphine	benzoylecgonine-D3	THC-COOH-D3	pentadeuterated analogues of the 5 analytes
Extraction type and conditions	solid phase, with Bondelut C18 columns (Varian)	solid phase, with Bondelut C18 columns (Varian)	solid phase, with NARC 1 SPE columns (Baker)	liquid/liquid, at pH = 13
Extraction or elution solvent	chloroform/isopropyl alcohol (90:10, v/v)	chloroform/isopropyl alcohol (90:10, v/v)	hexane/ethyl acetate (50:50, v/v)	chloroform
Derivatization reagent	BSTFA:TMCS (90:10, v/v)	BSTFA:TMCS (90:10, v/v)	BSTFA:TMCS (90:10, v/v)	TFA
Gas chromatographic column	HP 1, 12.5 m × 0.22 mm d.i. (Hewlett-Packard)	HP 1, 12.5 m × 0.22 mm d.i. (Hewlett-Packard)	HP 1, 12.5 m × 0.22 mm d.i. (Hewlett-Packard)	HP 1, 12.5 m × 0.22 mm d.i. (Hewlett-Packard)
Ionization and recording conditions	electron impact selected ion monitoring	electron impact selected ion monitoring	electron impact selected ion monitoring	electron impact selected ion monitoring
Detection limits (ng/mL)	6 MAM: 50 morphine: 30 codeine: 30 ethylmorphine: 30 pholcodine: 50	cocaine: 30 benzoylecgonine: 30 ecgonine-methyl-ester: 50	THC-COOH: 20	amphetamine: 50 methamphetamine: 50 MDA: 100 MDMA: 50 MDEA: 50

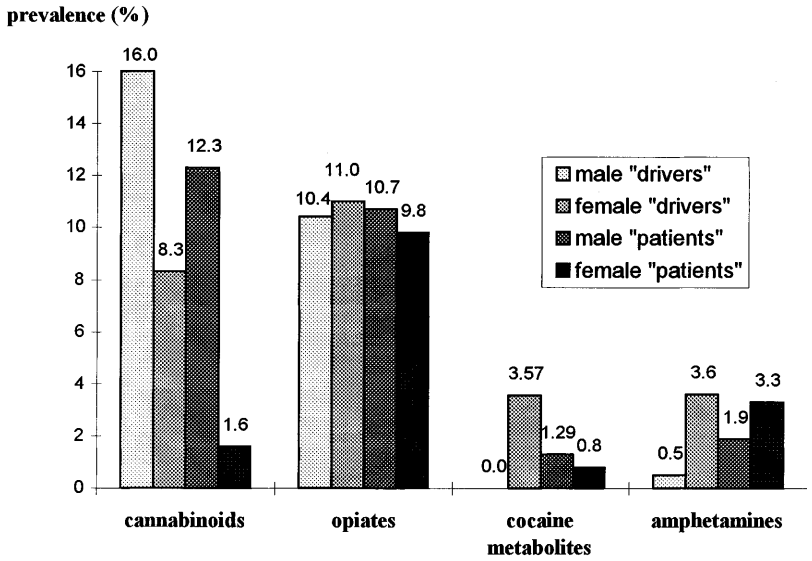

FIG. 2—*Prevalence of drugs of abuse in urine of male and female injured drivers and control patients.*

prevalence of cannabinoids was found in urine of males than in urine of females, in accident drivers (16.0% in males, 8.3% in females, $p < 0.05$) as well as in patients (12.3% vs. 1.6%, $p < 0.0001$). There was no difference in age between subjects positive and subjects negative for urinary cannabinoids, in any of these subgroups.

No difference was found between drivers and patients, or between males and females for the prevalence of urinary opiates. Nevertheless, a very significantly higher prevalence of opiates was found in male drivers, as well as in male patients positive for cannabis, than in cannabinoid-negative drivers or patients ($p = 0.003$ and $p = 0.001$, respectively). In female drivers and in female patients, this difference was not significant (Table 3).

Because of the limited number of positive results, no statistical comparison could be made between drivers and patients or within each group with regard to the prevalence of cocaine metabolites or amphetamines in urine (Table 3).

Discussion

This collaborative study demonstrated a high prevalence of cannabinoids in the urine of drivers involved in road accidents in France (13.9%), with twice as many cannabis users among men as among women. This is consistent with the results of a two-year survey of drug abuse in French troops (17), where cannabinoids were found in 13.6% of 5433 urine samples from conscripts aged 18 to 22. Furthermore, a previous collaborative study in France of the prevalence of cannabinoids, ethanol and benzodiazepines in a

population of 2938 injured drivers (7), close to ours with respect to sex ratio (29% of females) and age (mean age: 27.5 years), showed that 6.6% of blood samples (8.8% in men aged 20 to 35) were positive for tetrahydrocannabinol (THC). In North America, cannabinoids were reported in an even larger proportion of impaired drivers, or of drivers injured or killed in road accidents (4,5,10,13).

We also found a high prevalence of opiates in urine of injured drivers (approximately 10%), which may indicate licit or illicit use, which could not be differentiated in most cases. 6 MAM, the

TABLE 2—*Nature and occurrence of opiates and other associated drugs of abuse found in patients and drivers (*n = *60).*

	''Patients''		''Drivers''	
Nature of Opiates Found	Number of Samples	Associated Drugs of Abuse (Number of Samples)	Number of Samples	Associated Drugs of Abuse (Number of Samples)
6-MAM,* + morphine + codeine	1	− cocaine metab. (1)	2	− cannabinoids (1)
morphine + codeine	11	− cannabinoids (3) − cannabinoids + cocaine metab. (1) − amphetamine (1)	4	− cannabinoids + cocaine metab. (2)
morphine (alone)	6	− cannabinoids (1) − amphetamine (1)	11	− cannabinoids (4)
codeine and/or pholcodine and/or ethylmorphine (absence of 6 MAM* or morphine)	12	− cannabinoids (2) − cannabinoids + amphetamines (1) − cannabinoids + propoxyphene (1)	13	− cannabinoids (2)

* 6 MAM: 6-monoacetylmorphine, first metabolite of heroin.

TABLE 3—*Mean values of confounding factors, prevalence of drugs in urine and results of statistical comparisons between groups or subgroups.*

	Confounding Factors			Prevalence of Drugs of Abuse in Urine			
	Center	Sex (% of Males)	Age (years)	Amphetamines (%)	Cannabinoids (%)	Cocaine Metabolites (%)	Opiates (%)
			Inclusion status (''driver'' or ''patient'') as dependent variable				
In whole groups	NS	$p = 0.0001$‡	$p = 0.0160$*	NS	$p = 0.054$	NS	NS
# drivers = 296		(71.62)	(25.50)	(1.35)	(13.85)	(1.01)	(10.47)
# patients = 278		(55.76)	(26.46)	(2.52)	(7.55)	(1.08)	(10.43)
In males	NS		$p = 0.0931$	NS	NS	$p = 0.048$*	NS
# drivers = 212		...	(25.70)	(0.47)	(16.04)	(0.00)	(10.38)
# patients = 155			(26.65)	(1.93)	(12.26)	(1.29)	(11.00)
In females	NS		$p = 0.0719$	NS	$p = 0.0207$*	NS	NS
# drivers = 84		...	(24.99)	(3.57)	(8.33)	(3.57)	(10.71)
# patients = 123			(26.24)	(3.25)	(1.63)	(0.81)	(9.76)
			Sex as dependent variable				
In drivers	NS		NS	$p = 0.0359$	$p = 0.0425$*	$p = 0.0057$†	NS
# males = 212		...	(25.70)	(0.47)	(16.04)	(0.00)	(10.38)
# females = 84			(24.99)	(3.57)	(8.33)	(3.57)	(10.71)
In patients	$p = 0.0832$		NS	NS	$p = 0.0003$‡	NS	NS
# males = 155		...	(26.65)	(1.94)	(12.26)	(1.29)	(10.97)
# females = 123			(26.24)	(3.25)	(1.63)	(0.81)	(9.76)
			Cannabis status as dependent variable				
In male drivers	NS		NS	NS		NS	$p = 0.003$
# positive = 33		...	(26.68)	(0.00)	...	(0.00)	(26.47)
# negative = 179			(25.52)	(0.56)		(0.00)	(7.30)
In male patients	NS		NS	NS		NS	NS
# positive = 19		...	(26.05)	(5.26)	...	(5.26)	(36.84)
# negative = 136			(26.73)	(1.47)		(0.74)	(7.35)
In female drivers	NS		NS	NS		NS	NS
# positive = 7		...	(25.71)	(14.29)	...	(14.29)	(28.57)
# negative = 77			(24.92)	(2.60)		(2.60)	(9.09)
In female patients	NS		NS	NS		NS	NS
# positive = 2		...	(24.00)	(0.00)	...	(0.00)	(50.00)
# negative = 121			(26.27)	(3.31)		(0.83)	(9.09)

* Significant difference ($p \leq 0.05$).
† Highly significant difference ($p \leq 0.01$).
‡ Very highly significant difference ($p \leq 0.001$).

first heroin metabolite, was found in the urine of two drivers, but as 6 MAM is very rapidly metabolized into morphine, this figure may underestimate the real number of heroin addicts, as suggested by the detection of other illicit drugs in eight other drivers positive for opiates (Table 2). A previous study on 120 drivers hospitalized after road accidents in France reported 7% of urine and/or blood samples positive for opiates (8). This relatively high prevalence of opiates in accident drivers in France raises the question of their behavioral incidence on driving via their pharmacological impact on vigilance and psychomotor skills.

The prevalence of cocaine- and amphetamine-positive urine samples in both drivers and patients was low, ranging between 0 and 3.5%, according to drug and sex. In previous French studies of injured drivers, neither amphetamines nor cocaine were found (8,11). In the French army, amphetamines were detected in the urine of only 0.9% of 1404 regular soldiers; cocaine was not found in this population, but was detected in 0.06% of conscripts (17). Therefore, the abuse of amphetamines and cocaine seems to be of minor significance in France, at least in young adults. The situation is different in the United States where the prevalence of cocaine and amphetamines in impaired or killed drivers is much higher (6,12,14).

In order to implicate illicit drugs in road accidents, the best experimental scheme would be a prospective study, with long-term comparison of the rate of road accidents occurring in a population of drug abusers (''exposed'') and in a population of ''non-exposed'' drivers. This would, of course, be ethically unacceptable. To the best of our knowledge, such a study has only been conducted in a cohort of patients administered minor tranquilizers, which showed a trend to increased risk for accidents as compared to control subjects (18). Otherwise, a ''case-control'' study comparing the prevalence of drug use in drivers involved in a road accident and in non-accident drivers recruited at the scene and at time of the accident would address both the quantitative (prevalence) and qualitative (responsibility, evaluated by means of odds ratios) involvement of drugs in road accidents. Such a study, though, is difficult to implement, due to material and legal limitations. A Finnish study, concerning psychoactive licit drugs, compared injured drivers and drivers recruited in service stations (19). In other studies, drivers not at fault in their respective accidents were taken as controls for the drivers at fault (4,7,20); the one study conducted in France showed no significant difference between the two groups with respect to the prevalence of cannabinoids in blood. However, the probability of drivers being responsible for the accident increased with the combination of cannabis and alcohol, and even more with the combination of cannabis, alcohol and benzodiazepines (7). In this last type of study, the assessment of the responsibility of the driver in the accident is questionable and may weaken the statistical tests.

The control population in the present study could not be non-accident drivers, because they cannot be legally stopped and tested for drug use in the absence of an offense in France, nor accident drivers not at fault because the study was strictly anonymous, so it was impossible to study the circumstances of the accident or to access the police record. Therefore, a population of patients in the same age range, recruited in the same emergency departments and during the same period as drivers, was chosen as a comparative population. As drivers and patients were not matched for age and sex, mean age and sex ratio happened to be significantly different in these two groups. However, statistical analysis was adjusted for these differences which thereafter did not influence the comparison results. Some of the ''patients'' could have taken opiates for pain-relief and a few others might have been hospitalized because of their drug addiction (for infectious disease, withdrawal syndrome. . .), but we believe this possible overrepresentation of drug users in the comparative group does not represent a statistical bias in that it could only weaken but not refute the results of the statistical comparisons.

Other limitations of this study were the nature of the fluid chosen for drug testing and the lack of alcohol and therapeutic drug testing. An advantage of urine over blood, apart from non-invasiveness and ethical considerations, is a longer persistence and generally higher concentrations of drugs and metabolites, but this is also its major drawback as persistence ranges from one to several days, depending on the pharmacological class, that is to say, long after the pharmacological effect has vanished. Ethanol was not assayed in this study because urine ethanol level does not always reflect blood levels, depending on the time lapse between absorption and urine sampling, and because some of the laboratories were not equipped with gas chromatography for specific screening of ethanol. Sedative therapeutic drugs, such as benzodiazepines, barbiturates or meprobamate were not screened for, in order to limit the laboriousness and cost of the study and because interpretation of their presence would require knowledge of the medical history (usual treatment or occasional use?). For these reasons, the present results cannot directly imply the causal involvement of drugs in road accidents, but rather indicate the representation of drug users among injured drivers and in a comparative group.

Cannabis users were apparently overrepresented among injured drivers as compared to ''patients,'' but this difference was only significant in women, in spite of their small number. However, this finding should not be interpreted in terms of responsibility of cannabis in road accidents, inasmuch as urine samples were not assayed for ethanol, which is known to correlate with both road accidents and cannabis smoking. Nevertheless, the experimental administration of 300 μg/kg tetrahydrocannabinol by inhalation to volunteers has been shown to induce moderately impaired driving (3). Other studies have shown that cannabis lengthens reaction time and lowers attention skills (1), leading to psychomotor slowness which is obvious 4 h after drug use but might persist over 24 h. Furthermore, the changes in mood and behavior in the way of euphoria and de-inhibition, as well as the modification of perception abilities, could be as, or even more, important as the slowed reactions and sedation (21).

Conclusion

This study confirms the high prevalence of illicit drug use in the French young adult population. This is particularly true for cannabinoids, which were found in more than 10% of urine samples from 574 individuals aged 18 to 35. Opiates were also found in more than 10% of subjects but can correspond either to illicit consumption or to therapeutic use. However, the significant association of cannabinoids and opiates observed in both ''drivers'' and ''patients'' groups confirms a non-negligible prevalence of multi-drug abuse in young people.

Furthermore, our results demonstrate a higher prevalence of cannabinoids in urine samples of 84 female drivers involved in road accidents (8.3%) than in those of 123 female patients (1.6%) recruited in the same emergency rooms during the same period, and a trend to a higher such prevalence in male drivers than in male patients. This finding does not incriminate cannabis in road accidents, owing to the lack of ethanol measurements and to the

imperfect nature of the comparative group. However, it does underline the importance of cannabis consumption as social behavior in France, and the associated risk for driving cannot be excluded, even though the psychotropic effects of cannabis require further elucidation and are certainly less marked and harmful than those of other illicit drugs. Therefore, since the number of road accidents linked to any psychotropic drug use is directly related to the number of users, the question of cannabis and driving should be taken into consideration by legislators.

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