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Detection of illicit drugs in oral fluid from drivers as biomarker for drugs in blood

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ABSTRACT

Aim: To assess whether analysis of oral fluid can be used to identify individual drivers with drug concentrations in blood above 25 ng/mL for amphetamine and methamphetamine, 10 ng/mL for cocaine and 1.0 ng/mL for tetrahydrocannabinol (THC), which are the cut-off concentrations used in the European DRUID Project, by calculating the diagnostic accuracies when using the analytical cut-off concentrations in oral fluid as well as for the optimal cut-off concentrations.
Methods: Paired samples of whole blood and oral fluid collected with the Statsure Saliva.Sampler were obtained from 4080 drivers in four European countries and analysed for amphetamine, methamphetamine, cocaine and THC using GC-MS or LC-MS. The vast majority (89%) were random drivers not suspected of drug-impaired driving. Receiver-Operating Characteristic analysis was used to evaluate the analytical results.
Results: The prevalence of drug findings above the cut-off concentrations in blood was 1.3% for amphetamine, 1.0% for methamphetamine, 0.6% for cocaine and 1.3% for THC. The cut-off concentrations in oral fluid that gave the highest diagnostic accuracy were for amphetamine 130 ng/mL (accuracy 99.8%), methamphetamine 280 ng/mL (accuracy 99.9%), cocaine 570 ng/mL (accuracy 99.6%), and THC 38 ng/mL (accuracy 98.3%). The proportion of false positives were 0.2%, 0.1%, 0.1% and 0.9%; and the proportion of false negatives were 0.1%, 0.0%, 0.3% and 0.8%, respectively, when using those cut-offs. The positive predictive values were 87.9%, 92.9%, 84.6% and 35.7% for amphetamine, methamphetamine, cocaine and THC, respectively.
Conclusions: Analysis of concentrations of illicit drugs in oral fluid could not be used to accurately identify drivers with drugs concentrations above the selected cut-offs in blood in a cohort of drivers with low prevalence of drugs.

1. Introduction

Oral fluid (mixed saliva) can easily be collected in a non-intrusive manner. The use of oral fluid for diagnostic purposes is increasing; it can be used for the diagnosis of several diseases [1,2], to monitor exposure to chemicals [3,4], monitor therapeutic use of some drugs [5,6], and to detect recent use of illicit drugs [7–9]. On-site screening devices based on immunological methods are available for rapid screening of drugs in oral fluid [10,11], and positive findings are often used as reason for taking blood samples for quantification of drugs, particularly from drivers suspected for driving under the influence of drugs (DUID) [12].

The large inter-individual variations in the concentration ratios between drugs in oral fluid and blood (OF/B ratios) is a significant challenge when interpreting test results for oral fluid samples from suspected DUID offenders [13,14]; it makes it difficult to accurately assess whether the drug concentration in blood is high, based on a high concentration in oral fluid. This is partly related to the sampling process (e.g. type of sampling device), partly to variations in physiological factors affecting the transfer of drugs from blood to oral fluid (e.g. pH and flow rate of saliva) and the rate of transfer of drugs from blood to OF, and also affected by any contamination of drugs in the oral cavity due to snorting, smoking or oral drug intake, and the speed with which this is cleared.

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The Rosita-2 study of suspected DUID offenders found that testing of drugs in oral fluid had relatively good diagnostic accuracy when compared with testing of blood [15]. Similar results were found in another study of drugged drivers [16], whereas a more recent study of DUID offenders [17] and a study of random drivers [18] found lower positive predictive values (PPVs) for THC and cocaine than for amphetamine.

The aim of this investigation was to assess the ability to correctly identify individual drivers with drug concentrations in blood above the cut-off concentrations chosen by the European DRUID Project in a population of drivers with low drug prevalence in blood.

2. Materials and methods

Paired samples of whole blood and oral fluid were collected from 4080 drivers in Belgium ($n = 2750$), Finland ($n = 339$), Italy ($n = 891$) and Norway ($n = 100$). The vast majority of the included drivers (89.2%) were recruited in a roadside survey of drugs and driving performed as part of the Driving under the Influence of Drugs, Alcohol and Medicines project (DRUID) [19]. In order to increase the number of drug-positive drivers slightly, some drivers admitted to hospital after being injured in traffic crashes were included (8.3%), as well as some drivers who were suspected for DUID and therefore arrested by the police (2.5%). Oral fluid was collected by using Statsure Saliva.Sampler™ (Saliva Diagnostic Systems, Framingham, MA, USA). Whole blood was sampled using tubes containing potassium oxalate and sodium fluoride. The maximum time interval between sampling of blood and oral fluid was 30 minutes for each individual.

Samples were analysed for amphetamine, methamphetamine, cocaine and tetrahydrocannabinol (THC) by high performance or ultra-performance liquid chromatography with single or tandem mass spectrometric detection (LC-MS or UPLC-MS) or with gas chromatography with mass spectrometric detection (GC-MS) [20–24]. The analytical methods used by the four involved laboratories had different limits of quantitation and thus also different cut-off concentrations; therefore, the maximum analytical cut-off concentrations used by any of the laboratories were chosen for this study, see Table 1. No outlier test was performed.

We used Receiver-Operating Characteristic (ROC) analysis [25,26] to assess the analytical results. The numbers of true positives (TP), true negatives (TN), false positives (FP) and false negatives (FN) were used to calculate the sensitivity (SE = TP/[TP + FN] × 100%), specificity (SP = TN/[TN + FP × 100%], diagnostic accuracy (AC = [TP + TN]/[TP + TN + FP + FN] × 100%), positive predictive value (PPV = TP/[TP + FP] × 100%) and negative predictive value (NPV = TN/[TN + FN] × 100%). A TP was defined as a an observed drug concentration in oral fluid equal to or above the cut-off for an individual with a drug concentration in blood equal to or above the cut-off; whereas a FN was defined as an observed drug concentration in oral fluid below the cut-off for an individual with a blood drug concentration equal to or above the cut-off. TN and FP were defined similarly.

The optimal cut-off concentration in oral fluid, defined as the concentration that gave the highest possible diagnostic accuracy, was determined using ROC analysis.

3. Results

Of the included 4080 drivers, 1.7% were positive (≥ cut-off) for amphetamine in blood or oral fluid (1.3% in blood), 1.3% were positive for methamphetamine (1.0% in blood), 1.4% for cocaine (0.6% in blood) and 4.2% for THC (1.3% in blood). Many of the individuals with drug concentrations above or equal to the cut-offs in oral fluid had drug concentrations in blood below the cut-offs. As shown in Table 1, the proportions of false positives ranged from 0.3% for methamphetamine to 2.9% for THC. The proportions of false negatives were relatively low, from none for methamphetamine to 0.3% for THC. When using the analytical cut-off concentrations in oral fluid, the PPVs were 77.3% for amphetamine, 75.0% for methamphetamine, 34.7% for cocaine and 25.3% for THC.

ROC analysis was performed to determine the cut-off concentrations in oral fluid that gave the highest diagnostic accuracy. When using those cut-offs, the sensitivity ranged from 38.5% for THC to 100.0% for methamphetamine. The percentage of false positives among the 4080 analysed samples ranged from 0.1% for cocaine to 0.9% for THC; however, when calculating as fraction of the positive findings, the proportion of false positives was 12% (7 out of 58) for amphetamine, 7% (3 out of 42) for

Table 1
Test results when using the analytical and optimal cut-off concentrations in oral fluid.

	Amphetamine	Methamphetamine	Cocaine	THC
Analytical cut-off in blood and oral fluid, ng/mL	25	25	10[a]	1.0
Number of identified users[b], % (*N*)	1.7 (69)	1.3 (52)	1.4 (56)	4.2 (170)
Prevalence above cut-off in blood, % (*N*)	1.3 (54)	1.0 (39)	0.6 (24)	1.3 (52)
Prevalence above analytical cut-off in oral fluid, % (*N*)	1.6 (66)	1.3 (52)	1.2 (49)	3.9 (158)
False positive in OF, % (*N*)	0.4 (15)	0.3 (13)	0.8 (32)	2.9 (118)
False negative in OF, % (*N*)	0.1 (3)	0.0 (0)	0.2 (7)	0.3 (12)
Sensitivity, %	94.4	100.0	70.8	76.9
Specificity, %	99.6	99.7	99.2	97.1
Accuracy, %	99.6	99.7	99.0	96.8
Positive predictive value, %	77.3	75.0	34.7	25.3
Negative predictive value, %	99.9	100.0	99.8	99.7
Calculated optimal cut-off in oral fluid (ng/mL)[c]	130	280	570	38
Prevalence above optimal cut-offs in oral fluid (%)	1.4 (58)	1.0 (42)	0.3 (13)	1.4 (56)
False positive, % (*N*)	0.2 (7)	0.1 (3)	0.1 (2)	0.9 (36)
False negative, % (*N*)	0.1 (3)	0.0 (0)	0.3 (13)	0.8 (32)
Sensitivity, %	94.4	100.0	45.8	38.5
Specificity, %	99.8	99.9	100.0	99.1
Accuracy, %	99.8	99.9	99.6	98.3
Positive predictive value, %	87.9	92.7	84.6	35.7
Negative predictive value, %	99.9	100.0	90.7	99.2

[a] Data from Norway were not included because higher cut-off was used.
[b] Drug found in either blood or oral fluid.
[c] Optimised by ROC analysis for determining cut-off concentrations in oral fluid that predict the presence in blood with the highest possible accuracy.