Detection Times of Drugs of Abuse in Blood, Urine, and Oral Fluid

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Abstract: Data on the detection times of drugs of abuse are based on studies of controlled administration to volunteers or on the analysis of biologic samples of subjects who are forced to stop their (often chronic) use of drugs of abuse, eg, because of imprisonment or detoxification. The detection times depend mainly on the dose and sensitivity of the method used and also on the preparation and route of administration, the duration of use (acute or chronic), the matrix that is analyzed, the molecule or metabolite that is looked for, the pH and concentration of the matrix (urine, oral fluid), and the interindividual variation in metabolic and renal clearance. In general, the detection time is longest in hair, followed by urine, sweat, oral fluid, and blood. In blood or plasma, most drugs of abuse can be detected at the low nanogram per milliliter level for 1 or 2 days. In urine the detection time of a single dose is 1.5 to 4 days. In chronic users, drugs of abuse can be detected in urine for approximately 1 week after last use, and in extreme cases even longer in cocaine and cannabis users. In oral fluid, drugs of abuse can be detected for 5–48 hours at a low nanogram per milliliter level. The duration of detection of GHB is much shorter. After a single dose of 1 or 2 ng of flunitrazepam, the most sensitive methods can detect 7-aminoflunitrazepam for up to 4 weeks in urine.

Key Words: detection time, matrix, drugs of abuse

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Toxicologists are frequently asked how long a product or its metabolites can be detected after it was taken. It is often difficult to answer this question because the duration of detection depends on many factors, and few studies have focused on the detection time. Indeed, it is difficult to get approval for this kind of study because illicit products have to be given to healthy volunteers. Probably as a consequence of that, in many studies the administered doses are relatively low compared with street doses. There are also studies that measure the detection time of drugs of abuse after a complete stop of consumption, for example, in subjects imprisoned or admitted for detoxification. Even if these studies give invaluable information on detection times after use of often high quantities, they do not give information about the detection time after a single dose. We give an overview of the data on the detection time of amphetamine, methamphetamine, methylenedioxymethamphetamine (MDMA, ecstasy), cannabis, cocaine, opiates, LSD, and γ-hydroxybutyate (GHB). The data for blood (or serum or plasma), urine, and oral fluid are summarized in Tables 1–3, respectively. In these tables, the detection times are based as much as possible on the limits of quantification or detection of the methods, rather than on cutoffs. For flunitrazepam, some recent studies on the detection time after a single administration, as is the situation in cases of drug-facilitated criminal assault,[1–3] will be discussed. There are a few articles[4,5] that mention the detection time, and reviews on the detection times in urine[6] and oral fluid[7] have been published recently.

The detection time is influenced by many factors: the dose that was taken, the preparation and route of administration, acute versus chronic use, the choice of the matrix, the detection limit or cutoff of the analytic technique, the nature of the molecule or the metabolite sought, the pH and concentration of the urine or oral fluid, and the interindividual variation in metabolism.[6]

DETECTION TIME OF INDIVIDUAL DRUGS OF ABUSE

For each substance, the usual dose is given, as well as the detection times measured in blood (or serum or plasma), urine, and oral fluid.

Amphetamine

The usual dose of amphetamine is 10 to 30 mg, but tolerant subjects can take up to 2000 mg/d. The half-life is very variable and depends on the urinary pH: it varies between 7 and 34 hours.

In blood, amphetamine is detectable [limit of detection (LOD) 4 ng/mL] for 46 hours after the ingestion of 10 mg.[8]

If the pH of the urine is normal, approximately 30% of the ingested amphetamine is eliminated unchanged, but if the pH is 5, up to 74% is eliminated unchanged.[9] There are very few experimental studies on the detection time of amphet-

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TABLE 1. Typical Detection Times of Drugs of Abuse in Blood or Serum or Plasma

Drug	Dose (mg)/Route	Analyte	Cutoff (ng/mL)	Detection Time (hours)	Reference
Amphetamine	6/PO	Amphetamine	4	46	[8]
Methamphetamine	22/SM	Methamphetamine	3	48	[13]
MDMA	100/PO	MDMA	20	24	[16]
Cannabis	34/SM	THC	10	5	[21]
		THCCOOH	10	36	
Cocaine	100/IN	Cocaine	10	12	[32]
		Benzoylecgonine	10	48	
Heroin	12–20/SM	Morphine	1	20	[44]
GHB	4680/PO	GHB	5000	5	[54]

PO, oral; SM, smoked; IN, intranasal.

amine in urine after a single intake, but it is generally accepted to be 1 to 3 days. After a 5-mg dose of amphetamine, only 19% of the urine samples yielded a positive response (cutoff > 1000 ng/mL). After a 10-mg dose, 67% were positive, and after 20 mg, 88% were positive.[10] In a study in prisoners, the detection time was 4.8 days on average after the beginning of imprisonment, the maximum duration being almost 9 days.[11]

In oral fluid, amphetamine can be detected for 20 to 50 hours (LOD 10 ng/mL).[12]

Methamphetamine

The usual dose is 5 to 10 mg, but it can be much higher in tolerant subjects. Methamphetamine has a half-life that varies between 10 and 30 hours.

After smoking 22 mg of methamphetamine hydrochloride, methamphetamine remained detectable in blood (~3 ng/mL) for 48 hours, and amphetamine was 1 ng/mL after 48 h.[13]

After smoking of 22 mg methamphetamine as base ("Ice"), it remained detectable in urine (~300 ng/mL) for 60 hours.[13] After controlled administration of 10 mg of methamphetamine, the final detection time in urine after a single dose at the limit of quantification (LOQ, 2.5 ng/mL) was 87.2 ± 51 (extreme values 46–144) hours. At a cutoff of 500 ng/mL methamphetamine and 200 ng/mL amphetamine, it was 42.7 ± 22.8 (22–65) hours, and at half these cutoffs (250 ng/mL and 100 ng/mL, respectively) it was 51.6 ± 26.3 (25–77) hours.[14]

In oral fluid (obtained by stimulation with sour candy, with citric acid-treated and neutral cotton swabs), after intake of 10 mg sustained-release methamphetamine, it remained detectable for at least 24 hours (mean concentration 18.8 ng/mL). After 4 administrations of 10 or 20 mg, it was detectable for 36–72 hours.[15] The methamphetamine concentrations in oral fluid were between 2.3 and 4.3 times higher than those in plasma. The areas under the curve for methamphetamine oral fluid concentrations in samples collected with neutral cotton

TABLE 2. Typical and Maximal Detection Times of Drugs of Abuse in Urine

Drug	Dose (mg Unless Noted Otherwise)/Route	Analyte	Cutoff (ng/mL)	Detection Time (hours)	Reference	Maximal Detection Time (days)
Amphetamine						9
Methamphetamine	10/PO	Methamphetamine	2.5	87 ± 51	[14]	6
MDMA	100/PO	MDMA	20	48	[16]	
Cannabis	1.75%	THCCOOH	15	34	[23]	95
	3.50%/SM	THCCOOH	15	87		
Cocaine	100/IN	Benzoylecgonine	1000	48–72	[34]	22
LSD	0.28/PO	LSD	0.2	36	[42]	4
		2-Oxo-3OH-LSD	0.2	96		
Heroin	10–15 IV/SM	Morphine		11–54	[47]	11.3
GHB	100 mg/kg PO	GHB	10000	12	[53]	

PO, oral; SM, smoked; IN, intranasal; IV, intravenous.

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TABLE 3. Typical Detection Times of Drugs of Abuse in Oral Fluid

Drug	Dose (mg)	Analyte	Cutoff (ng/mL)	Detection Time (hours)	Reference
Amphetamine	PO	Amphetamine	10	20–50	12
Methamphetamine	10/SR PO	Methamphetamine	2.5	24	15
MDMA	100/PO	MDMA	126	24	17
Cannabis	20–25/SM	THC	0.5	34	24
Cocaine	25–42	Cocaine	1	5–12	38
	IV/IN/SM	Benzoylecgonine	1	12–24	
Heroin	20/IV	6-Acetylmorphine	1	0.5–8	7
Morphine	20/IM	Morphine	1	12–24	
GHB	4680/PO	GHB	4000	5	54

SR, sustained release; PO, oral intake; SM, smoked; IV, intravenous; IN, intranasal; IM, intramuscular.

swabs (mean oral fluid pH 6.0) were on average 1.47 times higher than those from citric acid-treated swabs (mean pH 2.8) and 1.31 times higher than those after citric acid candy stimulation (mean pH 4.3). With a neutral Salivette, the concentrations were 1.92 times higher than with citric acid candy.[15]

Methylenedioxymethamphetamine (MDMA, Ecstasy) and Derivatives

The usual dose varies between 50 and 100 mg. The half-life is approximately 7 to 8 hours. In a study in 2 volunteers, the administration of 100 mg of MDMA was detectable in blood (20 ng/mL) for 24 hours and in urine for more than 48 hours.[16] Twenty-four hours after the administration of 100 mg of MDMA to 8 subjects, the concentration was 13.5 [standard deviation (SD) 18.6] ng/mL in blood.[17]

The generally accepted detection time in urine is 1 to 3 days.[18] For MDEA (methylenedioxyethylamphetamine), the urinary detection time after administration of 140 mg varied between 1.4 and 2.6 days.[19] After administration of 100 mg of MBDB (methylbenzodioxazolylbutanamine), the detection time was 36 hours in urine (LOD 8 ng/mL) and 17 hours in oral fluid (LOD 2 ng/mL).[20]

Twenty-four hours after the administration of 100 mg of MDMA to 8 subjects, the concentration was 126.2 (SD 101.8) ng/mL in oral fluid (obtained without stimulation), approximately 10 times higher than in blood.[17]

Cannabis

The dose absorbed after having smoked a cannabis joint varies between 5 and 30 mg. The plasma concentration of tetrahydrocannabinol (THC) presents a very fast peak (about 3 to 8 minutes) and then decreases quickly (half-life of approximately 30 minutes). 11-Nor-9-carboxy-Δ^9-tetrahydrocannabinol (THCCOOH) has a much longer half-life, about 20 to 57 hours in occasional users and 3 to 13 days in regular users. THC is detectable (LOD 1 ng/mL) for approximately 5 hours in plasma and 10 hours in urine (LOD 10 ng/mL). THCCOOH can be detected much longer, and a detection time (LOD 5 ng/mL) of 25 days has been reported.[21] A study carried out in Lübeck with 52 volunteers admitted to a detoxification ward showed that THCCOOH (LOD 10 ng/mL) remained detectable in serum on average for 23.8 hours, and 49 hours to the maximum.[22]

After smoking a 1.75% or 3.55% THC cigarette, the last positive (15 ng/mL THCCOOH by GC-MS) urine sample was found at 33.7 ± 9.2 hours and 88.6 ± 9.5 hours, respectively.[23] After smoking marihuana, urine tested positive consecutively for average periods of 26 ± 9 (extreme values 2–72) hours with EIA and 33 ± 10 (extreme values 4–72) hours with GC-MS. The average THCCOOH detection times of the last positive specimen were 42 ± 10 (extreme values 2–72) and 58 ± 6 (extreme values 16–72) hours by EIA and GC-MS, respectively.[24] After a subject smoked a joint containing 1.75% THC, urine was positive (cutoff > 20 ng/mL, EMIT) for 2.1 days; after a joint with 3.5% THC, the detection time was 3.8 days.[23] Creatinine normalization of the THCCOOH values gives smoother excretion curves than THCCOOH concentrations alone, but even after normalization considerable variation between consecutive specimens remains.[25] Criteria were established for differentiating new drug use from residual excretion,[26] and these were evaluated by other authors.[27,28]

After oral intake, the detection time in urine seems to be longer, eg, after intake of 2 brownies containing 2.8% THC, the metabolite could be detected by EMIT (cutoff 20 ng/mL) for 5.9 days.[29] In chronic users, the inactive metabolite (THCCOOH) can be detected for weeks or even months.[25] The study by Lübeck in 52 volunteers admitted to a detoxification ward showed that THCCOOH (LOD 10 ng/mL) remained detectable in urine for 4.9 days on average and 18 days to the maxi-

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mum.[22] The longest reported detection times are 93 days[30] and 95 days,[31] but these are probably exceptional cases.

Niedbala et al measured the salivary concentrations of THC after oral administration or smoking of marihuana. The LOD were, respectively, 1 ng/mL and 0.5 ng/mL for ELISA and gas chromatography–tandem mass spectrometry (GC-MS-MS). All the analyses were positive for up to 15 hours (range 1–24) by ELISA and 13 hours (1–24) by GC-MS-MS. The detection times (last positive sample) were 31 hours (1–72) by ELISA and 34 hours (1–72) by GC-MS-MS.[24] In this study THCOOH was positive in urine for 58 hours (16–72 hours). However, the subjects were not supervised during the whole study, and some of them could have taken supplementary doses after supervision ended.

Cocaine

The usual intranasal dose varies between 20 and 100 mg, but it can be much higher in heavy users. The half-life of cocaine and benzoylecgonine are 1 and 6 hours, respectively. The detection time of cocaine in blood is 4 to 6 hours after 20 mg and 12 hours after 100 mg.[32] In serum, in chronic users, benzoylecgonine (BE; LOD 25 ng/mL) was detectable for 5.1 days on average (maximum 8.6 days).[22]

Benzoylecgonine, one of the main metabolites of cocaine, is positive in urine for 1 to 2 days after an intravenous administration of 20 mg.[33] After a higher dose (1.5 mg/kg) taken intranasally, the detection time is 2 to 3 days.[34] In a study of 18 individuals housed for up to 14 days on a closed research unit, benzoylecgonine equivalents were measured semiquantitatively by fluorescence polarization immunoassay (FPIA; cutoff 300 ng/mL). The mean time to the first negative specimen was 43.6 ± 17.1 (extreme values 16–66) hours. The mean time to the last positive specimen was 57.5 ± 31.6 (extreme values 11–147) hours after admission to the unit and 81 ± 34 (extreme values 34–162) hours after last admitted use. If creatinine normalization was used (with a cutoff of 300 ng BE equivalents/mg creatinine), the mean time to first negative was 88.4 ± 20.7 (20–100) hours, and the mean time to last positive was 88.4 ± 51.0 (35.6–235) hours.[35] After use of cocaine as a topical anesthetic and vasoconstricting agent in nasal surgery, benzoylecgonine was positive in all subjects after 24 hours but negative in all samples after 72 hours.[36] In the study by Lübeck in 52 chronic drug users, cocaine (LOD 50 ng/mL) was detectable for 6.8 hours on average (24.8 hours to the maximum), benzoylecgonine (LOD 50 ng/mL) for 47.4 hours (4.9 days to the maximum), and ecgonine methyl ester (LOD 50 ng/mL) for 35 hours (maximum 7 days).[22] In chronic users (who sometimes take more than 10 g per day), benzoylecgonine has been detected 22 days after the last consumption.[37]

In oral fluid, one can detect cocaine for 5 to 12 hours after a single dose.[7,38] By using methods able to detect 1 ng/mL, one can also detect benzoylecgonine for 12 to 24 hours. In chronic users, the detection time can reach 10 days (LOD 0.5 ng/mL).[39]

LSD

LSD is used in small doses (50–100 μg) and it is extensively metabolized. The half-life is approximately 2.5–5 hours. After a dose of 4 μg/kg of LSD, the peak LSD plasma concentrations were 7.4 and 9.7 ng/mL and fell below the LOD (5 pg/mL) after 24 and 48 hours.[40] Only 1% is excreted in the urine unchanged. After a typical dose, LSD is detectable in urine for 24 hours. The longest reported detection (after intake of 50 μg), measured by RIA at a 100 pg/mL cutoff, was 80 hours.[41] In urine, the peak LSD concentrations were seen after 10–12 hours and fell below the LOD (200 pg/mL) within 36 hours.[42] A few years ago, a new metabolite, 2-oxo-3-hydroxy-LSD, which is present in much higher concentrations in urine, was reported. Studies have shown that the mean ratio of 2-oxo-3-hydroxy-LSD to LSD is 42.9 (the median ratio was 16.1).[43] 2-Oxo-3-hydroxy-LSD could be detected in urine for up to 96 hours.[42]

Opiates: Heroin and Morphine

Heroin is most often injected or smoked. The dose used at the beginning is approximately 10 mg, but tolerant subjects can use up to 1 or 2 g. Typical half-lives of heroin, 6-acetylmorphine, and morphine are 2–7 minutes, 6–25 minutes, and 2–3 hours, respectively.

The detection time of morphine in blood (LOD 1 ng/mL) was 20 hours after intravenous administration of 12 or 20 mg heroin to a subject.[44] After smoking 10.5 mg of heroin, the detection time varied between 22 minutes and 2 hours.[44] After intramuscular injection of 20 mg of morphine, it was detectable (LOD 0.6 ng/mL) for 24 hours in plasma.[45] After administration of 9 mg heroin intranasally, morphine was detectable (LOD 1 ng/mL) in blood for 12 hours.[46] In the blood of chronic users, total morphine (LOD 25 ng/mL) was detectable for 29.2 hours on average (maximum 5 days), and free morphine (LOD 10 ng/mL) for 14.4 hours (maximum 5 days).[22]

After administration of 3, 6, and 12 mg heroin intravenously, 6-acetylmorphine is detectable in urine during respectively 2.3, 2.6, and 4.5 hours. Total morphine (LOD 300 ng/mL) is detectable for 18.5, 24.8, and 35.3 hours. After a lower than 7 mg dose, the detection time for total morphine (LOD 300 ng/mL) was 7.4 to 32 hours. For doses between 10 and 15 mg, the detection time was 11 to 54 hours.[47] In the Lübeck study, 6-acetylmorphine (LOD 10 ng/mL) was detectable for 5 hours on average (maximum 34.5 hours), and total morphine (LOD 25 ng/mL) for 4.95 days (maximum 11.3 days) in urine.[22] In a series of 63 male heroin addicts, morphine (detected by immunoassay) was positive in 88.4% after 1 day, 74.2% after 2 days, 64.2% after 3 days, 57.1% after 4 days, 63.3% after 5 days, and 44.8% after 6 days.[48]

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In oral fluid, 6-acetylmorphine is detectable (LOD 1 ng/mL) for 0.5 to 8 hours and morphine for 12 to 24 hours.[7] After intake of 60 or 120 mg of codeine, codeine was detectable by GC-MS for 21 hours in oral fluid at a cutoff of 2.5 ng/mL, and 7 hours at 40 ng/mL.[49]

Flunitrazepam: Detection Time after a Single Intake

The detection times of benzodiazepines are very variable because of their different pharmacokinetic characteristics. Recently, various authors used very sensitive methods to improve the detection time of flunitrazepam. After administration of 2 mg of flunitrazepam to 10 subjects, and by using a GC-MS method with negative chemical ionization (LOD for 7-aminoflunitrazepam 10 pg/mL), Negrusz et al could detect 7-aminoflunitrazepam in urine for 14 days in 6 subjects, 21 days in 1 subject, and 28 days in 3 subjects.[50] Kintz et al administered 1 mg and could detect 7-aminoflunitrazepam for 48 hours by liquid chromatography with diode-array detection, 72 hours by GC-MS with electronic impact, 96 hours by liquid chromatography-mass spectrometry or GC-MS in negative chemical ionization mode, and 120 hours by GC-MS-MS with negative chemical ionization.[51] In this study, the immunochemical methods never gave a positive result. Samyn et al detected flunitrazepam and 7-aminoflunitrazepam in oral fluid after administration of 1 mg of Rohypnol®. The detection time (LOD 50 pg/mL for flunitrazepam, 100 pg/mL for 7-aminoflunitrazepam) did not exceed 6 hours.[52]

γ-Hydroxybutyric Acid

γ-Hydroxybutyric acid (GHB) is eliminated very quickly (half-life of about 20 minutes). Because it is an endogenous product, it is necessary to use thresholds to differentiate an administration of the product from physiological concentrations. The following thresholds were proposed: EDTA-blood 5 μg/mL, postmortem blood 50 μg/mL, urine 10 μg/mL, and hair 2 ng/mg.[51] GHB can be detected for approximately 5 hours in blood and oral fluid and less than 12 hours in urine.[53] On the other hand, with a sweat patch, one can still detect supraphysiological concentrations 12 hours or 24 hours after the administration of 20 mg/kg of GHB.[54,51]

MINIMAL DETECTABLE AMOUNTS IN HAIR

In hair, the detection time depends on the length (the hair grows between 0.8 and 1.3 cm/mo). The most significant question is to know if a single administration of a product can be detected. There exist relatively little data. A single dose of 2 mg of flunitrazepam is detectable in the hair.[55] A dose of 3 mg of clonazepam was detected in 6 subjects out of 10.[56] For cannabis, the consumption of a joint (dose not mentioned) per week corresponds to a concentration from 0.02 to 3 ng/mg in hair. The consumption of a tablet (exact dose unknown) of MDMA corresponds to a concentration of approximately 0.5 ng/mg in hair, but in certain subjects, MDMA is not detectable. Experiments showed that the consumption of 0.6 mg/kg of cocaine is detectable in hair (communications at the workshop on hair analysis, Bordeaux, June 2001).

CONCLUSION

The detection times of abused drugs are extremely variable. The chances to detect the substances increase if the most sensitive methods are used (tandem-MS, negative chemical ionization), if one chooses the metabolite that persists longest, and if the biologic fluid that allows the longest possible detection time is available. In general, the longest detection times are found in hair, followed by urine, sweat, oral fluid, and blood. At a low nanogram per milliliter level, drugs of abuse can be detected in blood for 1 or 2 days, and in oral fluid for 5–48 hours. In urine the detection time of a single dose varies between 1.5 and 4 days. In chronic users, drugs of abuse can be detected in urine for approximately 1 week after last use, and in extreme cases even longer in cocaine (22 days) and cannabis users (up to 3 months). The duration of detection of GHB is much shorter. After a single dose of 1 or 2 ng flunitrazepam, the most sensitive methods can detect 7-aminoflunitrazepam for up to 4 weeks in urine. Many unknown factors remain, such as the time of detection of certain products after a single dose and the detectability of a single dose of a product by hair analysis.

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