



Adulteration of Urine Samples, Discovery and Mitigation

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Authors' contributions

This work was carried out in collaboration between all authors. Author BH designed the study and wrote the protocol. Authors BH and CB managed the chemical analyses. Authors BH and KB managed the literature searches. Author KB wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Purpose: In the field of urine drug testing, there are several strategies to manipulate a urine sample to become false negative and a wide variety of instructions and manipulation kits are offered on the internet. Some adulteration techniques for urine seriously disturb immunological drug tests but appear to have little effect on gas chromatography-mass spectrometry (GCMS). The present study aimed to evaluate the influence of different manipulants on drugs recovery using GCMS and the detection probability of drug disturbing substances by special test methods.

Methods: 16 different manipulation agents which are considered as effective were tested for their power when analyzing by GCMS. A sample check, an oxidant test, pH, creatinine-concentration, the Trinder sugar test and the Advia-check were taken as manipulation control tests. The recovery of 23 different drugs was determined, which correspond to the required proof by the German control regulations CTU, in concentrations within the range of the required limits.

Results: The effect of oxidants, such as chromate, hypochlorite, peroxide, nitrite and perchloric acid depends strongly on the pH-value of the sample. In untreated urine, their effect is rather low,

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only in combination with strongly acidic pH-values these chemicals develop their maximum impact. In addition to the oxidants, the analysis can also be disturbed by strong bases, such as caustic soda, strong acid or detergents (dishwashing liquid). These can be detected quickly by their suppression of the internal standard signals. Further investigation has shown that the effect of the adulterants can be reduced by adding buffer solutions and reducing agents to the sample immediately after urine delivery.

Conclusion: This study shows that there are just a few manipulators showing a significant influence on the GCMS result and they all can be detected by the selected tests on manipulators.

Keywords: Manipulation; drug analysis; urine; GCMS.

1. INTRODUCTION

Urine is one of the preferred matrices for drug abuse testing due to easy sample collection. In contrast to venous blood withdrawal, an important disadvantage of urine is the possibility of manipulation [1]. If the tested person expects a positive result, manipulations aim in a negative test result or a non-usable sample constellation. There are different manipulation strategies and a wide variety of manipulation kits is available on the internet [2,3,4,5]. A simple form of manipulation is dilution of the sample by adding water or, less conspicuously, drinking a lot, preferably in combination with a diuretic agent [6, 7]. The most effective way to manipulate is swapping the urine with clean urine. However, this is difficult under strict supervision or when using a marker system. Another form of manipulation is the adulteration of the urine with chemicals [2,3,4,8].

Chemicals can operate in different ways on the test result. One possibility is interfering with the test system so that the detection of drugs is no longer possible. The efficiency of this adulteration depends on the specificity of the test system [3]. The influence and mechanism of aspirin disturbing the EMIT drug test have been described by Linder and Valdes [9]. Several other papers also focused on the pitfall caused by substances on enzymatic drug tests of various manufacturers [2,3,5]. Another way of disguising a positive result is to destroy the drug, for example with oxidants [10,11,12]. In this case, the efficiency of adulteration does not depend on the testing system [3].

In the present study different adulteration substances, described as effective on immunologic assay systems in the literature [2, 13,14] were tested with a gas chromatography-mass spectrometry method (GCMS) and manipulation testing assays [15,8]. Furthermore, it was investigated whether chemicals added to

the urine collection system could affect the manipulation efficiency of chemicals [3,16].

2. METHODS

2.1 Materials

A QP 2010 Ultra GCMS from Shimadzu, Kyoto, Japan, and a VD-DA-column 12m/02 mm ID by Agilent Technologies, Santa Clara; USA were used for analysis of the samples. Sample preparation was performed by liquid/liquid extraction using Toxitubes A by DRG Instruments GmbH, Marburg, Germany.

Solvents of high purity p.a. and chemicals were purchased from Sigma-Aldrich GmbH, Munich, Germany. Reference substances and deuterated internal standards of Sigma-Aldrich Chemie Ltd. (Germany) were used.

For derivatization N,O-Bis(trimethylsilyl)trifluoroacetamid (BSTFA) was obtained from Macherey and Nagel, Düren, Germany. Commercially available dish soap was applied as an adulterant.

2.2 Analytical Techniques and Sample Preparation

The sample pools were prepared by spiking drugs into the clean urine. Two different urine pools with similar drug concentrations were investigated (Table 1). The chosen concentrations were near to the required low level of quantification concerning the German CTU (chemisch-toxikologische Untersuchung) criteria in driving qualification inquiry for people driving under the influence of drugs of abuse [17].

Manipulation agents (Table 2) were added to the two 3.5 ml samples and then incubated for three days at room temperature.

Table 1. Drug concentrations of the two urine-pools

Drug	Concentration (ng/ml)		Drug	Concentration (ng/ml)	
	Pool 1	Pool2		Pool 1	Pool2
Amphetamine	44,6	65	6-MAM	23,3	44
Methamphetamine	44,1	86	THC-COOH	6	13
MDA	43,9	68	Nordazepam	95,1	48
MDMA	42,8	74	Oxazepam	75	61
MDEA	39,6	67	Lorazepam	85,1	61
EDDP	44,7	43	OH-Bromazepam ¹	p	p
Methadone	38,6	80	Temazepam	119	68
Cocaine ¹	p	p	NH-Clonazepam ¹	p	p
Benzoylcegonine	72,5	59	NH-Flunitazepam	81,5	52
Dihydrocodeine	25,3	44	OH-Midazolam ¹	p	p
Codeine	24,2	50	OH-Alprazolam	98,6	65
Morphine	25,3	43			

¹ = qualitative measurement due to missing own deuterated internal standard.

As a check for sample integrity on the advia 1200 chemical analyzer from Siemens Healthcare, Erlangen (Germany), a modified test for methaqualone was used. Methaqualone is not used as a drug of abuse in Europe. To the reaction solution of the test, methaqualone was added to a resulting sample concentration of 200 ng/ml.

Each pool was analyzed 6 times, and the mean value of each agent concentration was used for further computation. The concentrations of the non-manipulated urine pools were set to 100%. As proposed in the guidelines for quality assurance in forensic toxicological investigations from the GTFCH (Gesellschaft für Toxikologische und Forensische Chemie) a deviation of 30% of the measured value from the spiked concentration is tolerable. Therefore, only a measured concentration which was lower than 70% of the original concentration was rated as an effective manipulation.

2.2.1 Sample preparation

3 ml urine and internal standard were filled into a Toxitude A from DRG Diagnostics Ltd. (Germany). The salt in the tube was shaken up and the tube mixed in an overhead stirrer for 5 minutes. After centrifugation, the organic layer was separated and completely dried under nitrogen. 75 µl BSTFA containing 1% TMS were added to the residue and then placed for 9 minutes in the microwave oven at 225 W. The samples were transferred into autosampler vials after cooling and 1 µl was injected into the GCMS. The liner temperature was 280°C, the column starting temperature was 85°C and rise to 280°C with a slope of 20°C/min. For quantification, a 7 point calibration was

performed. The calibration points were 20, 25, 30, 50, 75, 100 and 125 ng/ml for opiates, 25, 30, 40, 60, 80, 100 and 125 for benzoylcegonine, 8, 10, 15, 20, 25, 30, and 40 ng/ml for 11-Nor-9-carboxy- Δ^9 -tetrahydrocannabinol (THCCOOH) and 40, 50, 60, 75, 100, 150 and 200 ng/ml for the other substances.

2.2.2 Manipulants

The tested manipulants are shown in Table 2. These agents are known to disturb immuno assay drug screening tests [2,3,4,8].

Table 2. Manipulation agents per ml urine

Manipulation agents	
Dish detergent	10 µg
NaOH	10 mg
NaOH	100 mg
HCl	pH 1.25 in urine
Hypochloride	1%
H ₂ O ₂	1%
Chromate	10 mg
Nitrite	5 mg
NaCl	250 mg
Glutaric aldehyde	5 mg/ml
Acetic acid	10 mg
Vitamin C	50 mg
Boric acid:	50 mg
Perchloric acid 40%	20µl
Na ₂ S ₂ O ₃ :	15 mg
Phosphate buffer	pH 8 in urine

2.2.3 Adulteration tests

Creatinine, oxidants, pH-value, peroxides and adulteration tests were measured on an advia 1200 chemical analyzer from Siemens Healthcare, Erlangen, Germany. The "sample check" is an adulteration test using a cedia immuno assay (Thermo Fisher Scientific, Waltham, USA) and the advia check is an in-

house adulteration test for the Siemens EMIT assay.

Also, it was tested whether the oxidation power of the oxidants was lowered if 100 µl of a 0,1 molare phosphate buffer pH 8 and 15 mg/ml reducing reagent Na₂S₂O₃ were added to the urine about one minute after the oxidants.

3. RESULTS

3.1 Chemicals Disturbing Immuno Assay Drug Screening

In Table 3 the results for the adulterants NaCl, glutaric aldehyde, acetic acid, vitamin C and boric acid are shown. For each adulterant, the recovery of the analytes is presented in percent of the non-manipulated urine pools. Analytes which have not been significantly affected by any of these adulterants are not listed.

Vitamin C and boric acid were detected by both adulteration check tests, glutaric aldehyde only by the "sample check" and NaCl only by the advia check. Acetic acid and vitamin C showed a low pH-value. Only these two adulterants have a significant influence on the measured concentration of the drugs.

Samples mixed with acetic acid showed a reduced recovery rate (48% to 69%) for

diazepam metabolites oxazepam, desmethyldiazepam, and temazepam. If vitamin C was added, in addition to the diazepam metabolites amphetamine, amino-clonazepam was found in lower concentrations 34% to 60% and hydroxy-bromazepam could not be detected.

3.2 Oxidants

The effect of oxidants can be depicted from table 4. The oxidation test was positive for peroxide, nitrite, and chromate but not for hypochloride. The pH was only decreased if chromate was added. The "sample check" detected peroxide and chromate and the advia check detected only chromate. Hypochloride showed no detectable influence on drug analysis. Hydrogen peroxide reduced the recovery of methadone, morphine, 6-monoacetyl-morphine, amino-clonazepam and amino-flunitrazepam up to 42%. In the presence of nitrite, the concentrations of amphetamine, methadone, amino-clonazepam and amino-flunitrazepam were decreased to 25% and THC-COOH was negative. Chromate showed the strongest influence on drug analyses. All analytes in Table 3 were detected in smaller amounts or negative as amphetamine, 6-monoacetyl-morphine, hydroxy-bromazepam, amino-clonazepam, and amino-flunitrazepam. The internal standards, if used, were negative (6-mam and amphetamine), too.

Table 3. Effects of NaCl, glutaric aldehyde, acetic acid, vitamin C, and boric acid on adulteration tests (upper part) and recovery of the drugs, expressed in percent of the non-manipulated urine

Adulterant	Not present	NaCl (250 mg/ml)	Glutar-aldehyde (5 mg/ml)	Acetic acid (10 mg/ml)	Vitamin C (50 mg/ml)	Boric acid (50 mg/ml)
Sample Check (%)	100	91	72	90	86	81
Creatinine (mg/dl)	104	97	85	97	105	92
Oxidants	0	0	0	0	0	0
pH	5,7	5,8	5,3	2,9	2	5,7
Trinder-reaction (mg/dl)	6	6	6	6	0	6
Advia-check (%)	100	77	100	86	71	66
Amphetamine (%)	100	98	112	83	60	80
Nordazepam (%)	100	83	84	48	34	88
Oxazepam (%)	100	80	92	69	43	87
OH-Bromazepam ¹	p	p	p	p	n	p
Temazepam (%)	100	91	93	69	32	93
NH-Clonazepam (%)	100	93	105	73	58	95

¹ =: no own deuterated IS, n = not detected, p: positive. bold characters = recovery rate was below 70%

Table 4. Effect of the oxidants hypochloride, hydrogen peroxide, chromate and nitrite on adulteration tests (upper part) and recovery of the drugs, expressed in percent of the non-manipulated urine

Adulterant	Not present	Hypo-chloride 1%	Peroxide 1%	Chromate 10 mg/ml	Nitrite 5mg/ml
Sample Check (%)	100	88	45	38	98
Creatinine (mg/dl)	104	104	87	95	99
Oxidants	0	0	42	511	453
pH	5,7	6,9	5,7	2,2	5
Trinder reaction (mg/dl)	6	6	3800	14	5,2
Advia-Scheck (%)	100	101	99	<> MB	90
Amphetamine (%)	100	123	125	n *	68
EDDP (%)	100	91	72	58	100
Methadone (%)	100	94	63	56	54
Benzoyllecgonine (%)	100	102	122	61	100
Morphine (%)	100	105	56	16	77
6-MAM (%)	100	100	46	n	71
THC-COOH (%)	100	100	77	15	n *
Nordazepam (%)	100	98	97	41	86
Oxazepam (%)	100	92	98	67	87
OH-Bromazepam ¹	p	p	p	n	p
Temazepam (%)	100	96	102	65	94
NH-Clonazepam ¹	p	p	p	n	p
NH-Flunitrazepam (%)	100	98	42	n	25

¹ =: no own deuterated IS, n = not detected, p: positive. bold characters = recovery rate was below 70 %

3.2 Influence of pH-Value and Detergents

In Table 4 adulterants disturbing sample preparation is shown like dish soap, Drano (NaOH), NaOH (100 mg/ml) and hydrochloric acid.

All drugs including the internal standard could not be detected if dish soap was added to the urine. The sample shows abnormal behavior at sample preparation procedures. The sample check was the only adulteration test which detects dish soap. The advia check shows a normal value but also the drug tests were positive with the EMIT test in the presence of dish soap. The opiates, THC-COOH hydroxy-midazolam, and hydroxy-alprazolam are not decreased in the presence of NaOH. The other analytes decreased with increasing NaOH concentration. At higher NaOH concentrations most of the drugs were negative.

The amphetamines, benzoyllecgonine, THC-COOH and most of the benzodiazepines were negative or had lower concentrations if the sample pH was reduced to 1.2.

3.3 Effect of pH and Reducing Agents on Manipulation with Oxidants

The effect of oxidants in an acidic environment is shown in table 6. The effect of oxidizing agents can be modulated by variation of the urinary pH-

value. The oxidative efficiency of hypochloride, chromate, nitrite, hydrogen peroxide and perchloric acid is increased if the pH-value decreases, which is to be expected for a redox reaction.

Amphetamines, THC-COOH and most of the opiates and several benzodiazepines were destroyed by nitrite, chromate and hydrogen peroxide. The internal standards of several opiates and THC-COOH could not be detected using nitrite and chromate as adulterants.

The most effective destruction of drugs was the use of nitrite, hydrogen peroxide and chromate under acidic conditions. The efficiency of oxidation should be lowered if the urine is collected in a cup containing a buffer and a reducing reagent like sodium sulfite (Na₂S₂O₃). The results are shown in Table 6. Only the detection of THC-COOH and some benzodiazepines are still interrupted by chromate and nitrite. But the color of the chromate containing urine turns into green in the presence of sodium sulfite, so chromates should be easily detected.

4. DISCUSSION

The present results are in line with other studies showing that the effect of adulteration reagents on the detection by GCMS after extraction with Tox tubes A is lower than on an immuno assay

[2,3,4,8]. However, a negative result was obtained with oxidants and dish detergent which interfered with sample preparation. Oxidation is facilitated in the presence of hydrogen ions. Therefore, it should be carried out under the acidic condition to enhance the oxidative effect of the oxidants used in the present study [18]. The most powerful oxidants are chromate, and nitrite but even they were not able to destroy all drugs after an incubation time of three days at room temperature. That even holds if low drug concentrations below the immuno assay cut off were used from 10 ng/ml THC-COOH to 100 ng/ml for some benzodiazepines. Our method does not allow for structure analysis of the oxidized drug. Therefore, any statement about the concrete point of molecular oxidative action would be highly speculative. Anyway, all

chemical adulterations which lead to a negative result could be detected at least by one of the adulteration tests if the pH-value was measured, the analysis known as "sample check" or the Advia test reaction was performed and an oxidation test was used for adulteration testing. It could be shown that chemical manipulation has a high risk to be detected [19] and, therefore, it appears not to be a really big problem in drug analysis. A more safe way to get negative urine test results after drug consumption is to swap the urine [5]. The effect of chemical manipulation can be reduced if the urine is collected in a cup with a buffer and a reducing agent like sodium sulfite, which can be crystallized at the border of the cup. This application is difficult to recognize and, therefore, it hardly will be spilled out by the user.

Table 5. Effect of dish cleaner, NaOH and HCl on adulteration tests (upper part) and recovery of the drugs, expressed in percent of the non-manipulated urine

Adulterant	Not present	Dish cleaner (10µg/ml)	Drano; NaOH (10%)	NaOH (100 mg/ml)	pH 1,25
Sample Check / %	100	0	0		
Creatinine mg/dl	104	98	69		
Oxidants	0	0	0	-6	0
pH	5,7	5,8	13,5	>14	1,2
Trinder reaction mg/dl	6	6	9	35	4
Advia-check / %	100	102	< MB	35	89
Amphetamine (%)	100	n *	n *	n *	n *
Methamphetamine (%)	100	n *	92	n *	n *
MDA (%)	100	n *	77	n *	n *
MDMA (%)	100	n *	115	n *	n *
MDEA (%)	100	n *	97	n *	n *
EDDP (%)	100	n *	23	20	85
Methadone (%)	100	n *	n *	69	111
Cocaine ¹	p	n	n *	n	p
Benzoyllecgonine (%)	100	n *	n *	n	n *
Dihydrocodeine (%)	100	n *	102	99	88
Codeine (%)	100	n *	136	126	102
Morphine (%)	100	n *	112	141	75
6-MAM (%)	100	n *	57	125	74
THC-COOH (%)	100	n *	92	88	n *
Nordazepam (%)	100	n *	50	n *	47
Oxazepam (%)	100	n *	18	n *	10
Lorazepam (%)	100	n *	31	n *	n *
OH-Bromazepam ¹	p	n	n	n *	p
Temazepam ¹	p	n	p	n *	p
NH-Clonazepam (ng/ml)	100	n	51	n *	n
NH-Flunitrazepam (%)	100	n *	n	n *	22
OH-Midazolam ¹	p	n	p	p	p
OH-Alprazolam (%)	100	n *	92	92	34

¹ = no own deuterated IS, n = not detected, n * = not detected and no internal standard found, p: positive (no quantification). If the recovery rate was below 70 % the value is printed in bold characters

Table 6. Effect of the oxidants hypochloride, hydrogen peroxide, chromate and nitrite after pH reduction to 1.25 with hydrochloric acid on adulteration tests (upper part) and recovery of the drugs, expressed in percent of the non-manipulated urine. Compared to the effect in the presence of a buffer (b) and sodium sulfite (r) as reducing agent

	Not present	pH1.25+b	Chromate	Chromate +b+r	Nitrite	Nitrite +b+r	Perox.	Perox. +b+r
Oxidants	0	0	456		453		183	-1
pH	5,7	5	1,25	5	1,25	5	1,25	
Trinder reaction	6	4	8		5,2		15319	0
Advia check	367	90	0		92		92	65
Amphetamine (%)	100	111	n *	112	n *	107	94	108
Methamphetamine (%)	100	107	n *	98	n *	89	94	115
MDA (%)	100	105	n *	113	n *	133	98	105
MDMA (%)	100	107	n *	100	n *	84	91	84
MDEA (%)	100	112	n *	110	n *	108	85	88
EDDP (%)	100	107	110	83	96	57	81	72
Methadone (%)	100	116	96	114	111	112	102	92
Cocaine ¹	p	p	p	p	p	p	p	p
Benzoylcegonine (%)	100	60	96	92	n *	71	117	116
Dihydrocodeine (%)	100	103	n	98	94	103	93	94
Codeine (%)	100	110	n	69	89	102	112	99
Morphine (%)	100	93	55	104	56	22	105	93
6-MAM (%)	100	101	n	54	n	27	80	91
THC-COOH (%)	100	n *	n	n *	n	n *	n *	46
Nordazepam (%)	100	48	n	68	13	97	37	51
Oxazepam (%)	75	81	n *	92	42	104	n *	41
Lorazepam (%)	100	97	n *	102	72	102	19	68
OH-Bromazepam ¹	p	p	n *	p	n *	p	n *	n *
Temazepam ¹	100	p	n *	p	p	p	p	p
NH-Clonazepam ¹	p	p	n *	n *	p	n *	p	p
NH-Flunitrazepam (%)	100	94	30	17	9	n *	65	77
OH-Midazolam ¹	p	p	p	n *	n *	p	p	p
OH-Alprazolam (%)	100	95	62	94	n	96	67	57

¹ means: no own deuterated IS, n: not detected, n *: not detected and no internal standard found, p: positive (no quantification).
If the recovery rate was below 70 % the value is printed in bold characters

5. CONCLUSION

Chemical manipulation is hardly a safe way to produce a negative result for drug testing in urine when GCMS detection in combination with sample manipulation tests is used. Thus, it is not really suspected to be a real serious problem for drug testing. Swapping the sample with clean urine may be the more reliable way to get a negative result if supervised sample collection is not strict enough or no urine marker system is being used.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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