

Urine labeling with orally applied marker substances in drug substitution therapy

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Abstract

The compliance of 581 drug addicts attending six methadone substitution outpatient clinics was determined over a period of 18 months. Urine from these patients was labeled following oral administration of low molecular weight polyethylene glycols as marker substances. These substances were measured in approx. 5800 urine samples. A protocol for applying marker substances and ways to prevent substitution of urine samples were evaluated. Normal values for marker substances in urine were determined. The results suggest that this labeling procedure is a new diagnostic tool to prevent manipulation of urine samples by drug addicts receiving substitution therapy.

Keywords: drugs of abuse; enteral labeling substances; patient compliance; polyethylene glycols.

Introduction

Patient compliance in adhering to the regular intake of prescribed drugs can be a serious problem in many clinical situations. In many cases, doctors cannot rely on the validity of patient self-reporting. Extremely poor patient compliance is expected in the testing for possible intake of drugs of abuse (DOA) in the therapy of drug addicts on methadone substitution.

This substitution therapy is usually accompanied by measuring DOA concentration in urine (1). There are several reports indicating that frequent drug tests from urine are essential and that patient self-reporting alone is not a reliable indicator (2–7). A high percentage of drug addicts is suspected to have an interest in false-negative data (8) in DOA testing. Patients who have consumed illicit drugs may fear loss of take home privileges or discharge from the treatment program.

There are several documented methods of tampering with urine samples: dilution by drinking excessive amounts of water or external dilution, adulteration by mixing the urine with oxidants, soaps etc., or substitution of urine with “clean” samples. The term “clean” usually means free of any drugs of abuse. In the case of drug addicts undergoing substitution therapy with methadone, “clean” urine is assumed to contain methadone and its metabolites.

There is an entire industry, mainly based in the USA, distributing materials that are designed for manipulating results of urine tests. Many of these techniques can be uncovered with modern methods of clinical chemistry. Urines can be routinely checked for pH, creatinine, nitrite and specific weight by the sample check reaction (9) and by other recommended methods (10).

Substitution of urine by a “clean” sample, however, remains a serious problem. There is a market for “clean” urine samples in Germany with an average price of 25 € for a “clean” methadone-containing urine sample (11). To combat this problem of sample substitution, it is advised to closely monitor patients while urinating (12).

In this report we describe a new labeling procedure that allows us to clearly identify the urine sample as coming from a particular patient. It is based on methods used to determine malabsorption in pediatric medicine (13). Our first attempt was to modify tests originally designed for determining malabsorption for the enteral labeling procedure. A large variety of sugars and other substances have been described in the literature for oral absorption tests, with the xylose absorption test (14) being the most commonly used to date.

As many sugars can appear in urine of healthy individuals in significant quantities, difficulties would arise in interpreting results. For this reason and because of difficulties with the analytical set-up, we decided to use low molecular weight polyethylene glycols as marker substances.

Marker substances are taken orally prior to providing the urine sample. Patients are then allowed to urinate without supervision. Urine samples are traced to

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the patient by determining the presence of marker substances previously ingested.

In our foregoing study we have described the selection of marker substances by testing a variety of substances with healthy volunteers. A test system for these substances was evaluated (15).

Materials and methods

The following drug outpatient clinics and patient numbers were included in the study:

• Gesundheitsamt Düsseldorf, Methadon-ambulanz:	162 patients
• Rheinische Kliniken Essen, Methadon-ambulanz:	74 patients
• Rheinische Kliniken Köln, Methadon-ambulanz:	110 patients
• Klinik Marienheide, Drogenentgiftung:	16 patients
• Rechtsrheinisches Drogenhilfenzentrum:	122 patients
• Verein Krisenhilfe Essen, Methadonambulanz:	97 patients

The total number of patients recruited in this study was 581. Sixty percent of the patients were males. The average age was 30 years with an average time of treatment of 4 years. The daily dose of methadone ranged from 50 to 120 mg methadone with an average of 80 mg.

The study lasted from July 2000 to January 2002. In this period, approximately 11,200 urine samples were investigated for drugs of abuse and 5796 urine samples were sent to the laboratory for marker substance determinations.

Patients were given a solution of polyethylene glycols and sucrose. In most cases the individual methadone dose was included. Patients had to wait for 30 min and were then allowed to provide urine without supervision. After this period, the urine sample was labeled and sent to the laboratory.

The reference method in all cases was direct inspection of patients while urinating. For validation of negative results of marker substance determinations, patients had to be accompanied while urinating the next day.

The following marker substances were used:

- 1 g polyethylene glycol 300 (Merck, Darmstadt, Germany), Marker A
- 2 g polyethylene glycol 600 (Merck), Marker B
- 1 g polyethylene glycol 300 and 2 g polyethylene glycol 600 (Merck), Marker C

The polyethylene glycol preparations used are certified for in vivo use by the manufacturer. Low molecular weight polyethylene glycols are applied in pharmacy as a solvent for drugs, for example in cough mixtures.

The following DOA analyses are routinely offered by the Central Laboratory Cologne:

- Amphetamines
- Barbiturates
- Benzodiazepines
- Cocaine metabolites, i.e., benzoylecgonine
- 2-Ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP); metabolite of methadone
- Methadone
- Opiates
- THC metabolites, i.e., 11-nor- Δ^9 -carboxy-tetrahydrocannabinol

Tests for DOA were performed with reagents from Microgenics, Passau, Germany, on an automatic Hitachi 911 ana-

lyzer from Roche, Mannheim, Germany. For cleaving glucuronic acids from benzodiazepines, 0.3 U-glucuronidase/arylsulfatase from *helix pomatia* (EC 3.2.1.31 and EC 3.1.6.1; Merck, Darmstadt, Germany) and 0.5 U of a recombinant β -glucuronidase from *E. coli* (EC 3.2.1.31; Roche, Mannheim, Germany) in 20 μ l 2 mol/l sodium acetate buffer pH 4.8 were added to 1 ml urine and incubated for 30 min at room temperature prior to investigating for benzodiazepines. Urine samples that were positive for opiates were retested on the Remedi system, an automatic HPLC equipment purchased from BioRad, Munich, Germany. Suspicious samples were also occasionally retested on a gas chromatography/mass spectrometry (GC/MS) system (Hewlett Packard, 5790 Series II, connected with a mass selective detector 5972; Hewlett Packard, Palo Alto, USA) according to a procedure described elsewhere (16). For sample preparation, Bond Elute-Certify (130 mg/3 ml) solid-phase extraction columns from Varian Inc. were used. The extraction procedures were carried out as described in the Certified Methods manual by Varian Germany GmbH, Darmstadt.

Urines were further investigated for:

- Creatinine (17),
- Sample check reaction (9),
- Methyl-4-hydroxybenzoate (MHB) (15),
- Sucrose.

Urines were also occasionally checked for pH, glucose, protein, hemoglobin and nitrite with a Multistix 10SG in an automated Clinitec Atlas System from Bayer Vital (Fernwald, Germany).

To measure sucrose concentration, 3 μ l urine was first incubated with 50 μ l of 48 μ g/ml invertase (46 U/ml) (EC 3.2.1.26) (Sigma, Deisenhofen, Germany, EC 3.2.1.26, Grade VII, 960 U/mg) in citrate/phosphate buffer pH 4.5. The mixture was incubated at 37°C for 5 min. Then 350 μ l of the glucose reagent (18) prepared as described by Sigma was added. The absorbance was measured at 505 nm at the beginning and after 5 min of incubation at 37°C. Calibration was done with 2–500 μ mol/l sucrose solutions. This protocol was applied to a Hitachi 911 analyzer. Urines positive for sucrose were retested for glucose without pre-incubation with invertase by automatic reflex testing. Only urines that were positive for sucrose and negative for glucose were reported "positive" for sucrose.

Patients had to sign a written agreement prior to participating, indicating the type of substance used and the purpose of the study.

Marker substances and 10 mg MHB were mixed with Coca Cola or with a solution of 20 g sucrose, dissolved in 100 ml of tea or coffee, etc. Patients were asked to drink this solution 30 min prior to delivery of urine. They were then allowed to urinate without supervision.

After patients handed over the urine sample (20–50 ml), the tube was directly identified with a bar code label according to the routine procedure of the Central Laboratory Cologne. An accompanying order sheet was labeled with the patient's name, the type of DOA analyses requested and the type of marker substance that was used. Samples were then sent to the Central Laboratory Cologne via post or through the shuttle service of the Central Laboratory Cologne.

In the Central Laboratory, order sheets were read by an automatic chart reader. Urine samples were centrifuged and directly transported to the analytical site for determination of marker substances and DOA.

The entire protocol was certified by the Commission of Medical Ethics of the Municipal Hospital Cologne, Germany

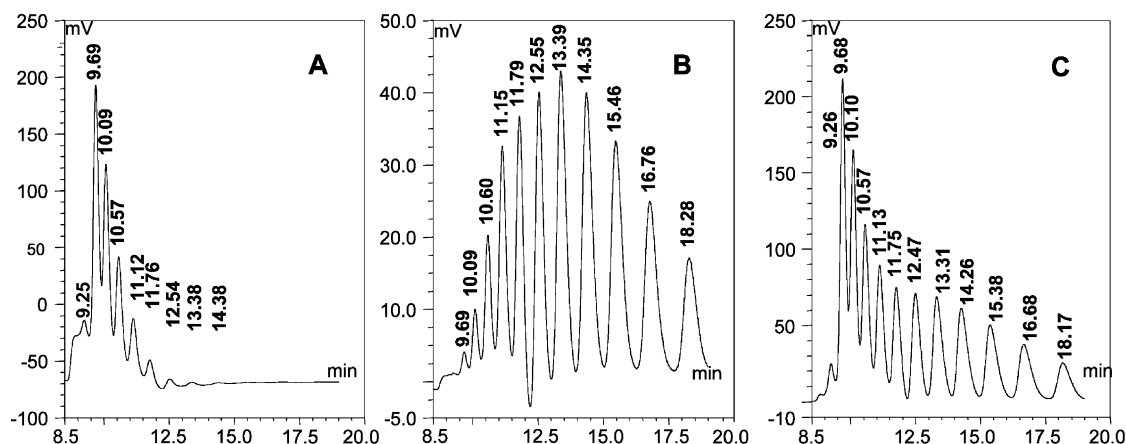


Figure 1 Chromatograms of polyethylene glycols from urines. Patients were given 1 g (Marker A), 2 g (Marker B) or 3 g (Marker C) polyethylene glycol. After 30 min they were allowed to deliver urine without supervision. Patient urines were chromatographed on Nucleosil C18 and C8 in 45% aqueous methanol as described elsewhere (15).

and the Ethic Committee of the University Clinic Essen, Germany.

Results

Three marker combinations were developed for this study:

- Marker A: 1 g polyethylene glycol of average molecular weight 300
- Marker B: 2 g polyethylene glycol of average molecular weight 600
- Marker C: mixture of Markers A and B

These markers can be identified by pattern analysis of the resulting chromatograms in HPLC (see Figure 1). No disturbance of the drug confirmation analysis was observed on the Remedi system or the GC/MS in sim or scan mode if marker substances were present in urine samples.

Patients were fully informed of the new labeling procedure and asked to sign a written consent for the study procedure. All patients were free to choose either intake of marker substances or supervision while urinating.

Two patients were identified with a prolonged excretion time, their urine only being positive for marker substances after 45 min. These patients, therefore, provided urine after a wait of 45 min.

We quantified the concentrations of polyethylene glycols in the urine of patients by analyzing the peak areas of the HPLC chromatograms (Figure 1) in comparison to external standards. Results are shown in Figure 2. Marker A appears between 100 and 1500 $\mu\text{g/ml}$ in 96.4%, Marker B between 120 and 1500 $\mu\text{g/ml}$ in 96.9%, Marker C between 140 and 1500 $\mu\text{g/ml}$ in 96.9%.

The reported values were described as "negative", "no material", "too little material", "positive" or "marker X found instead of given marker Y". The data on polyethylene glycol concentrations allowed us to assume "normal values" of $> 100 \mu\text{g/ml}$ for Marker

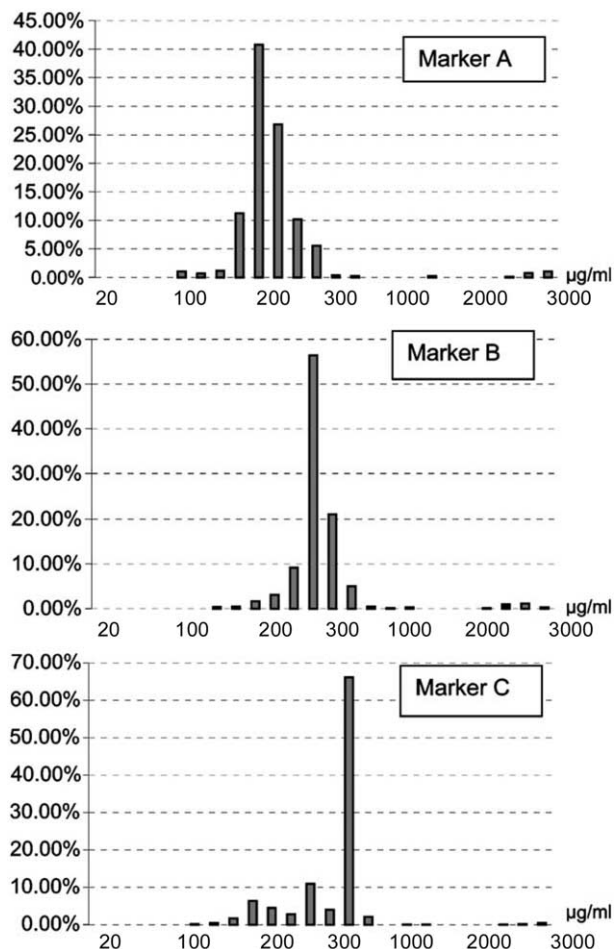


Figure 2 Frequency distribution of polyethylene glycols in urine. Approximately 1900 urine samples each from patients who were given 1 g (Marker A, $\mu\text{g/ml}$), 2 g (Marker B, $\mu\text{g/ml}$) or 3 g (Marker C, $\mu\text{g/ml}$) polyethylene glycols 30 min prior to delivery of urine samples, were determined for polyethylene glycol contents. Polyethylene concentrations were quantified according to external calibration standards.

Table 1 Data on the marker determinations from the urines of drug addicts.

Patients, n	Urines analyzed, %	Reports
29		Wrong material sent to the laboratory
31		Urine sent to the laboratory, but no marker applied
2		Too little urine sent to the laboratory
3	0.05	Strongly diluted urines as indicated by low creatinine
5	0.09	Positive for sucrose
83	1.45	Marker other than the ingested marker
5471	95.4	Positive for the marker applied
172	3.0	Negative
5796	100	Total

A, >120 µg/ml for Marker B and >140 µg/ml for marker C (samples below are regarded "negative").

From 5796 urine samples that were sent in for marker substance determination, 5734 were investigated, amounting to almost 99%. Data are summarized in Table 1.

Four different types of attempts to falsify the outcome of the marker substance determinations were documented or discussed in the course of the study:

Type 1 One patient used a sample of another patient's urine from the toilet. This came to light because the marker combination of the patient's urine should not have been identical to the urine of the foregoing patient. We found other markers than those applied in 1.45% of all cases, indicating that there were a significant number of attempts to falsify the results of the marker determinations with this type of method.

Type 2 One patient admitted that he had spat marker substance into "clean" urine from another patient, thus bypassing his body. We added sucrose (conventional "sugar") and 4-hydroxybenzoic-acid-methylate (15) to the solution for oral application and determined concentrations of these substances in urine. Sucrose and 4-hydroxybenzoic-acid-methylate are metabolized in the human body and do not appear physiologically in urine.

Type 3 There are several reports describing the destruction of DOA molecules or the disturbance of the immunoassays by incubating urines with acids, alkalines, peroxides, chromates, nitrites, glutaraldehyde, detergents or other compounds (19–21). We very rarely find urines that test positive for the sample check reaction. No positive reactions were found in the course of this study.

Type 4 There may be a chance of diluting a patient's urine with water or in a more sophisticated manner with "clean" urine that has been smuggled into the toilet. This manipulation method would then aim to find a dilution window in which markers are still found, whereas DOA cannot be determined. For all urines assessed in this study, we calculated the dilution factor that would yield a DOA concentration just lower than the detection limit of the method for determining DOA in urine. Then we divided the marker concentrations by these factors, individually calculated for each urine sample, containing DOA and markers. These factors vary from 1.2 up to 5 with no preference for any marker or DOA. From this we calculated the maximum percentage of samples that under optimal conditions might be negative for DOA but still positive for markers. As outlined in Table 2, there is a maximum percentage ranging from 7.06% with marker C for benzoylecgonine to 37.7% for 11-nor- Δ^9 -carboxy-tetrahydrocannabinol with marker C. Data are given in percent for all positive samples.

A dilution "error" of 50% would lower the probability below 5% for most of the drugs and below 8% for cannabinoids.

In this study, we had no knowledge of the use of this method of manipulation. It may be that some of those samples that were reported as "negative" for marker substances included urines that were unsuccessfully manipulated by the Type 4 method.

Discussion

The data presented here suggest that the new labeling procedure is a useful diagnostic tool to determine patient compliance in drug substitution therapy. It avoids the humiliating experience of direct supervision of urination. The analytical procedure can easily be installed in any well-equipped clinical chemical

Table 2 Maximum percentage of samples negative for DOA but still positive for marker substances, which can be achieved by dilution of patient's urine with water or "clean" urine.

	Benzo-diazepines	Cocaine-m	Opiates	THC-m
Detection limit (ng/ml) of the method	160	239	239	30
Marker A	10.2%	7.35%	16.0%	33.3%
Marker B	8.9%	14.1%	11.5%	34.1%
Marker C	14.6%	7.06%	11.0%	37.7%

For explanation see text.

laboratory. German health authorities have assured us that European certification procedures (ISO 9001, EN 46001, IEC 60601/1) do not apply to this method. For Europe, there are no legal restrictions for installing the labeling procedure as described in this publication.

In this study, we discriminated between four manipulation methods: urine switching (Type 1), body bypassing (Type 2), adulteration (Type 3) and dilution with water or "clean" urine (Type 4).

Type 1 Urine samples may still be manipulated with this method by hitting upon the correct marker combination when substituting urine from another patient. The likelihood of a successful manipulation is 33%. We plan to increase the number of marker substances since three markers are too limiting. Monodisperse polyethylene glycols are available because of increasing demand by the chip industry. Our laboratory is now undergoing a certification procedure that will allow us to produce up to 100 different marker combinations from monodisperse products in the future.

Type 2 We now use two different classes of markers: one of which is metabolized to monitor body bypassing (methyl-4-hydroxybenzoate and sucrose) and one that is not metabolized (polyethylene glycol). The quotient of the molar concentrations of sucrose in the marker solution to the limit of detection is higher than that of polyethylene glycol. It is therefore impossible to yield urine positive for markers but negative for sucrose by adding a certain amount of marker solution into "clean" urine. However, even after the laboratory communicated that urines are checked for sucrose and MHB, some patients still tried this procedure (Table 2).

Type 3 With the exception of cannabis, DOA tests are disturbed by most adulterants at concentrations that also significantly change the signal of the sample check reaction (3, 19–21). Peroxides are sometimes effective in altering DOA molecules and difficult to determine. They can, however, now be detected in very low concentrations by a false-positive signal in the glucose-Trinder reaction that we originally introduced for determining glucose after invertase treatment.

Since the detection of cannabis abuse would not lead to any therapeutic consequence in drug outpatient clinics, we did not apply more validity tests. In other fields, however, such as workplace testing, a lot more validity tests need to be performed (4).

Type 4 Manipulating urine samples with this method would mean diluting urine with a distinct volume of water or "clean" urine. This may yield urine samples in which DOA are not detectable but in which markers may still be determined. The probabilities for successfully tampering with urine samples by dilution with this method (Table 2), however, are very theoretical considering the situation of a drug addict alone

in a toilet. The optimal dilution factors arise from determinations in the laboratory and are principally unknown to the patient. Thus a person trying to falsify results by diluting his urine with water or "clean" urine takes a rather high risk of being detected.

Are there still other ways avoiding DOA detection with this new method? Judging from the feedback from our patients, there would appear to be none. We still emphasize, however, that some supervision of the patients should take place so that opportunities to manipulate urine samples for DOA analysis are not unlimited.

When data on the marker concentrations were communicated as "negative", doctors were asked to repeat the test on the next day since errors cannot be excluded.

- in some cases doctors or nurses had forgotten to add the markers;
- sometimes patients had waited less than 30 min;
- two patients had a prolonged excretion time for polyethylene glycols.

If data on the marker concentrations need to be used for forensic purposes, supervision and documentation are required to prove that the markers have really been ingested. To be on the safe side, the time between marker ingestion and urine sampling should then be fixed at 45 min.

Although the data from this study support the idea that the new labeling procedure allows matching of urine samples to patients, it is premature to judge its full clinical significance for drug outpatient clinics.

A number of questions need to be answered

a) Are there patient complaints? Do patients change to another drug outpatient clinic because of treatment with the new labeling procedure?

b) Is the new labeling procedure easily incorporated into the daily routine of a drug outpatient clinic? Which organizational problems arise with the labeling procedure?

The number of participants in this study is too small to fully answer these questions, and the data presented here should therefore be regarded as preliminary.

a) To our surprise, the patients' reactions were positive in general. None of the patients changed to another outpatient clinic because of the demands of this study. One outpatient clinic stated that some patients would prefer to be supervised while urinating rather than take the marker substance. However, the staff of this outpatient clinic claimed that complaints regarding the urinating procedure decreased considerably after the installation of the new labeling method.

b) Of the six outpatient clinics, one did not continue the marker substance labeling after this study because of organizational problems. In this outpatient clinic there is only a limited time frame of 2 hours in the morning for treatment and medical support of the patients. Nurses and doctors decided that the labeling procedure is too time-consuming. They still uphold a

system in which patients are allowed to urinate without supervision and urine is controlled for temperature.

In all other outpatient clinics, the response of doctors and nurses was positive. These outpatient clinics continued to use marker substances after the end of this study.

Conclusions

It is a general impression that the new procedure cannot be installed without changes in the organizational pattern of the daily routine. The waiting time of 30 min must be incorporated into the therapeutic schedule of the outpatient clinic. This waiting time can be used for physical examination of the patients and for psychological therapy. Many doctors reported that therapeutic concepts can now be installed more easily because discussions on the validity of DOA measurements are not that necessary any more.

Urine tests in therapy of drug addicts are sometimes described as a "black box" (6). There are almost no guidelines other than general remarks that doctors have to assure themselves that the urine is coming from the patients' body. The diagnostic procedures differ from *laissez-faire* to extremely strict supervision. Our new method will therefore be probably received differently according to the different concepts for diagnosis and therapy in each drug outpatient clinic.

This labeling procedure may be one more diagnostic tool in the hands of therapists. Of course it cannot replace plausibility controls, which are based on the general clinical impression of the patient and on psychological guidance. Our method may not only be used in therapy of drug addicts but also for the control of the intake of prescribed drugs, doping controls and in any other clinical situation where doctors need to control patient compliance.

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