

Efficacy of a Polyethylene Glycol Marker System in Urine Drug Screening in an Opiate Substitution Program

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Key Words

Opiate dependence · Methadone substitution · Drug screening · Polyethylene glycol marker

Abstract

Aims: Screening for concomitant drug consumption is necessary in opiate substitution therapy of opiate-dependent patients. Adulteration of samples is a common problem in this setting. A recently developed polyethylene glycol marker system allows reliable identification of urine samples. In this study, we aimed to compare the rates of drug detection in conventional and marker urine samples. **Design:** This cross-sectional evaluation was performed in an ambulatory opiate substitution program. We studied 55 opiate-dependent patients (32 men, 23 women). In all patients we compared the rates of drugs detected in the marker urine with the most recent conventional urine control. Additionally we assessed the rate of marker urine manipulation. **Findings:** In the conventional urine controls, opiates and benzodiazepines were found in 3.6 and 27%, respectively, whereas in the marker urine controls, these rates were 33 and 40%, respectively. Signs of urine manipulation were present in 35%. The rates of concomitant consumption and urine manipulation were higher among the patients without than among

those with take-home substitution. **Conclusions:** With the marker urine, an unexpectedly high prevalence of concomitant consumption can be found. Marker urine testing has a significantly higher sensitivity for the detection of concomitant drug use.

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Introduction

One of the aims of opiate replacement therapy for opiate-dependent patients is to stop the use of illegal drugs, especially heroin. Concomitant consumption of other psychotropic substances such as benzodiazepines, which exert additional respiratory depressant effects, will increase the risk of morbidity and mortality [1, 2]. Nevertheless, simultaneous intake of benzodiazepines is very common among opiate-dependent patients [3, 4]. Concomitant consumption of illegal drugs can best be controlled by drug screening in urine samples. Drug screening is also particularly important for determining which patients are eligible to receive prescriptions for the sub-

stitution drugs allowing them to get the substitution drug from a pharmacy for several days (take-home agreement). Only patients proven to be free of concomitant drug use are potentially eligible for a take-home agreement. Adulteration of urine specimens is a common problem in this setting. To avoid it, strict supervision of urine sampling is recommended [5]. However, this method is not only time-consuming but also stressful for both patients and medical staff. Additionally, it is not completely reliable either.

Recently, an orally ingestible marker system for urine samples has been developed [6, 7]. It uses biologically inert low-molecular-weight polyethylene glycols that are rapidly excreted with the urine after oral ingestion. This allows a reliable identification of urine samples.

The aim of this study was to compare the rates of illegal opiate and benzodiazepine use as detected by conventional laboratory diagnosis. We compared the rate of urines positive for illicit drugs from patients after ingestion of the polyethylene glycol marker and patients with only conventional urine controls including sporadic visual urine controls. Additionally, we aimed to assess the rate of attempted marker urine manipulation in a typical opiate substitution outpatient clinic.

Patients and Methods

We studied 55 opiate-dependent patients (32 men, 23 women; age [mean \pm SD] = 36.4 \pm 8.1 years, substituted for 24.3 \pm 20.3 months in our outpatient clinic). All patients attended the Opiate Substitution Outpatient Clinic of the Hospital München-Schwabing. Thirty-seven patients were substituted with methadone (82.0 \pm 41.1 mg), 10 received levomethadone (41.0 \pm 12.7 mg), and 8 were substituted with buprenorphine (9.8 \pm 6.9 mg). A proven lack of concomitant consumption of illegal drugs in our outpatient clinic for at least 1 month is one of the prerequisites for a take-home agreement. Of the studied patients, 22 had a take-home agreement prior to marker urine testing. All marker and conventional urine controls were part of clinical routine and all patients gave informed consent.

For the marker urine controls, the patients ingested a solution of low-molecular polyethylene glycols dissolved in 200 ml of lemonade. Thirty minutes after ingestion they were asked to deliver urine without supervision. To allow for correct urine identification, 1 of 3 available polyethylene glycol markers with different molecular weights were given to the patients in a random fashion. The patients did not know the molecular weight of the solution they received. Renal secretion of the marker substance peaks after 30 min. Thus, it was possible to identify if the patient had ingested the marker and thus not adulterated the urine sample. All samples were shipped at room temperature and measured at the RUMA central laboratory in Cologne.

The marker substances were measured with isocratic reversed-phase high-performance liquid chromatography. The opiate and

benzodiazepine concentrations were determined with a semi-quantitative immunoassay.

Conventional urine controls were done routinely every second week in all patients in the Opiate Substitution Outpatient Clinic of the Hospital München-Schwabing. Of these, a sporadic visual control was carried out on average every sixth time. In the conventional urine controls, opiate and benzodiazepine detection was done with a qualitative immunochromatographic test (MP; Rapid Diagnostics, Burlingame, Calif., USA).

We assessed the rates of benzodiazepines and opiates detected in marker urine controls and compared them to the most recent conventional urine control (within 3 weeks prior to marker urine control) in the same patients. If the results were discrepant, this was considered as a sign of previous urine manipulation. If the correct marker could not be detected or substances in the marker urine made drug measurement impossible, this was regarded as manipulation of the marker urine. These cases were not counted for the calculation of the percentage of drug detection in the marker urine samples.

To compare between the groups, we used the unpaired, 2-sided Student t test with a p value \leq 0.05 considered significant.

Results

With the conventional urine controls, we found opiates and benzodiazepines in 3.6 and 27% of the patients, respectively. With the marker urine controls, the rates of opiates and benzodiazepines were 33 and 40%, respectively. A discrepancy between the most recent conventional urine and the marker urine was present in 29% of the patients. In all cases of discrepancy, either benzodiazepines or opiates or both were found in the marker urine but not in the conventional urine. In 5% (3 patients), we observed signs of marker urine manipulation. Of these 3 patients, in 2 cases, marker was not detectable in the urine sample, and in another case, there was sugar in the urine. Taken together, any sign of urine manipulation was present in 35% of the patients.

Figure 1 displays the rates of drug detection and signs of manipulation among the total group and among the patients with and without previous take-home agreement. As can be seen, both rates of detected drugs and signs of manipulation were higher among the patients without take-home agreement.

The patients with signs of urine manipulation were younger than those without (33.1 \pm 6.6 vs. 38.1 \pm 8.3 years; $p = 0.027$), but there was no significant difference in time of substitution (19.6 \pm 16.4 vs. 26.6 \pm 21.8 months; $p = 0.21$). Among the patients with manipulation there were 37% women and 11% received buprenorphine. Of the patients without signs of manipulation, 44% were women and 17% received buprenorphine. In the patients

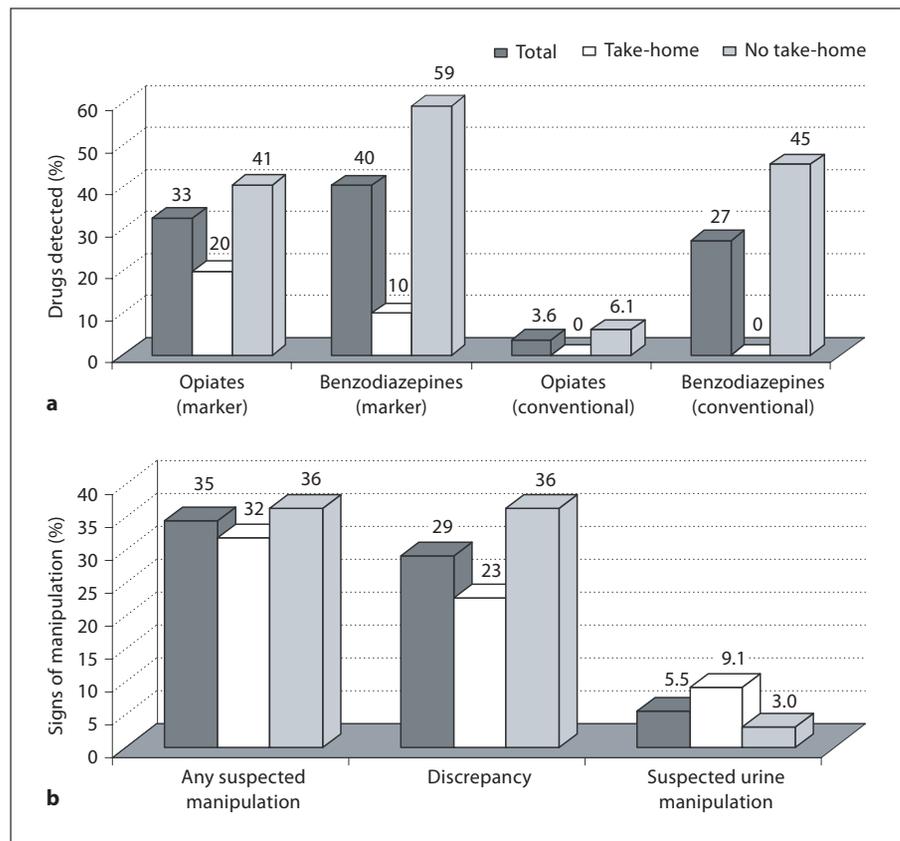


Fig. 1. Percentages of drug detection (a) and signs of manipulation (b) in all patients and with regard to take-home agreement.

substituted with methadone or levomethadone, there was no significant difference in content of substituted bioactive levomethadone among those with and without signs of manipulation (36.0 \pm 13.3 vs. 26.8 \pm 21.8 mg, respectively; $p = 0.18$; fig. 1).

Discussion

In this study we have found that the rate of concomitant benzodiazepine use detected with the marker system is about 1.5 times higher than that determined with conventional urine controls. Yet more strikingly, an even 10-fold higher rate of concomitant opiate abuse has also been detected with the marker system. In more than one third of all patients, indications of urine manipulation are present.

Conventional urine testing was performed up to 3 weeks before marker urine evaluation. We cannot exclude with absolute certainty that some patients had no concomitant use during the first urine test and new simultaneous intake during the second test and, thus, not

manipulation was the cause of discrepancy. However, this seems unlikely, since, in case of discrepant results, conventional urine samples were always negative, whereas marker urine samples were always positive. Nevertheless, we counted discrepant results as indication rather than proof of manipulation.

Our results show that conventional urine screening clearly underestimates the rate of concomitant drug abuse in substituted patients. It is of particular interest that also one third of patients with a take-home agreement have indication of urine manipulation, implying that these patients have been eligible for a take-home regulation on the false assumption that they were drug free.

The rates of suspected urine manipulation were slightly higher in the non-take-home than in the take-home group. Whereas it is clear that patients with take-home prescription are motivated to mask their concomitant drug consumption in order to avoid loss of take-home eligibility, these results indicate that also patients without take-home prescription are highly interested in masking any simultaneous intake. Possible reasons for this might

include a future interest in receiving take-home prescriptions, and the fear of 'disappointing' the treating physicians and nurses.

The use of polyethyleneglycol markers has been proven to be easy to perform, safe and reliable [6, 7]. Applying

this marker, our preliminary data indicate that the prevalence of undetected concomitant drug consumption in ambulatory replacement therapy is much higher than previously assumed. Further studies in larger samples are desirable to confirm these results.

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