

Evaluation of intoxication in patients with acute impaired consciousness using rapid urine test tape; a diagnostic accuracy study

Behrooz Hashemi¹, Zahra Eshghi², Amir Ghabousian³, Saeed Safari^{4*}

1 Research Center for Trauma in Police Operation, Directorate of Health, Rescue and Treatment, Police Headquarter, Tehran, Iran.

2 Emergency Medicine Department, School of Medicine, Shohadaye Tajrish Hospital, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

3 Road Traffic Injury Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

4 Men's Health and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Corresponding author: Saeed Safari; Email: s.safari@sbmu.ac.ir

Published online: 2022-06-19

Abstract: **Objective:** Determining the exact underlying etiology of loss of consciousness (LOC) can become a real challenge for physicians due to the broadness of differential diagnoses. The current study aimed to assess the accuracy of a commercially available strip for urine drug screening, in patients presenting with LOC.

Methods: One hundred fifty patients with LOC were enrolled in the current cross-sectional study. The diagnostic accuracy of a multidrug urinary strip rapid test was evaluated in comparison to blood analysis as the reference test, and the screening performance characteristics of the rapid test for each substance were estimated.

Results: The average age of patients was 46.21±18.59 years (72.67% male). The most frequent false positive results of the test were related to Benzodiazepine (21.5%), Methamphetamine (7.5%), and Tramadol (5.4%), respectively. The screening performance characteristics of the test tape were the best in detection of Amitriptyline with 100.0% (95% CI: 30.99 – 100.0) sensitivity, Cocaine with 100.0% (95% CI: 5.46 – 100.0) sensitivity, and Methadone with 91.54% (95% CI: 81.88 – 96.51) sensitivity, respectively.

Conclusion: The current study reveals that employing a urinary strip test for detecting drug intoxication in the setting of emergency department can lead to significant false positive and negative results. Accordingly, relying on a urine drug screen to determine the underlying etiology of LOC should be done with caution.

Keywords: Diagnosis; Emergency Service, Hospital; Illicit Drugs; Substance Abuse Detection

Cite this article as: Hashemi B, Eshghi Z, Ghabousian A, Safari S. Evaluation of intoxication in patients with acute impaired consciousness using rapid urine test tape; a diagnostic accuracy study. *Front Emerg Med.* In Press.

1. Introduction

Loss of consciousness (LOC) is a relatively frequent cause of referrals to the emergency department (ED) (1). Given the vast array of differential diagnoses, determining the exact underlying etiology could become a real challenge for physicians (2, 3). The underlying causes of impaired consciousness (IC) can be classified into two main categories, namely neurological and non-neurological (4, 5). Substance abuse and misuse are among the most common non-neurological causes of LOC, which have been escalating alarmingly throughout the world (6, 7). In order to reach a definitive diagnosis in the ED, a clinician might require taking account of medical history, physical examination, imaging, laboratory testing, and response to antidote for the reversal of intoxication (8, 9). However, there is a lack of an antidote for the majority of abused drugs. Therefore, when obtaining a reliable history from patients or witnesses is impracticable and the clinical examination is not leading the way, drug screening methods can take priority over the

strategies mentioned above (10). Immunoassay-based urine drug screening could be employed as a simple, cost-effective, and non-invasive method for rapid detection of drugs and their metabolites (11). However, false positive test results induced by cross-reactivity and false negatives due to urine concentrations beneath the diagnostic cut-off point can mislead the emergency clinicians (12). Besides, even in the absence of clinically effective serum levels of a substance, urinary excretion could last for a specific period (13). To avoid any misinterpretation, being au fait with the screening performance characteristics of drug testing is of the essence. Thus, the present study aimed to evaluate the accuracy of a commercially available strip for urine drug screening in patients presenting to ED with LOC.

2. Methods

2.1. Study design and setting

The current cross-sectional study recruited patients with an acute alteration of mental status presenting to the emergency

departments of Shohadaye Tajrish and Loghman Hakim Hospitals during one year. The diagnostic accuracy of a multirug urinary strip rapid test was evaluated based upon confirmatory blood testing. The Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran approved the study protocol (IR.SBMU.RETECH.REC.1401.015). All the measures taken in this study complied with the Declaration of Helsinki. After briefing the patients or their relatives on the study objectives, they signed written informed consent forms for participation.

2.2. Study population

All adults aged over 18 years presenting to the cited hospitals' emergency departments with acute reduction in level of consciousness were included. The convenience sampling method was used to select the subjects. The excluded subjects comprised those who were unwilling to participate or unable to give informed consent. Decisions on how to manage the study patients were not related to the urine test results.

2.3. Data collection

The data were collected using a checklist comprising demographic information, baseline characteristics, vital signs upon arrival, time of admission, method of patient transfer to hospital, underlying diseases, urine drug test results, and confirmed laboratory diagnosis regarding the intoxication. All the patients received initial care. Afterwards, a senior resident collected their data and interpreted their urine test results. Their confirmed diagnosis regarding the presence or absence of intoxication was recorded after receiving the results of their blood tests.

2.4. Measurements

The immunoassay-based urine rapid test strips (manufactured by ABON Biopharm Company) were used to screen for cocaine, amphetamine, methamphetamine, marijuana, methadone, morphine, tramadol, benzodiazepines, amitriptyline, and buprenorphine. The diagnostic accuracy of this method was assessed in comparison to the results of the confirmatory toxicological analysis of the blood samples using gas chromatography/mass spectrometry (GC/MS).

The test strip, immersed in the patient's fresh urine sample for 10 seconds, was removed and placed on a non-absorbent dry surface for 5 minutes, and the results were then interpreted. The emergence of a single line in the control area or two separate lines were respectively interpreted as positive and negative urine test results. Emergence of no lines or a single line at the bottom of the strip suggested an invalid test, which was repeated.

2.5. Statistical analysis

The data were analyzed in SPSS-19. The sample size calculated as 144 based on the results of a study by Grossman using $\alpha=0.05$, $d=0.1$ and sensitivity=0.9, was ultimately considered

Table 1 Baseline characteristics of studied cases

Variables	Number (%) / mean \pm SD
Level of triage (ESI)	
I	29 (19.3)
II	97 (64.7)
III	23 (15.3)
IV	1 (0.7)
Signs of trauma	
Yes	24 (16.0)
No	126 (84.0)
Hallucination	
Visual	9 (6.0)
Auditory	6 (4.0)
None	135 (90.0)
Focal neurologic deficit	
Yes	0 (0.0)
No	150 (100.0)
Loss of consciousness	
Sudden	66 (44.0)
Gradual	82 (54.7)
Fluctuant	2 (1.37)
Opioid withdrawal symptoms	
Yes	13 (8.7)
No	137 (91.3)
Pupil size	
Normal	76 (50.7)
Miosis	54 (36.1)
Mydriasis	20 (13.3)
Pupillary light reflex	
Normal	59 (39.3)
Abnormal	91 (60.7)
Level of consciousness (GCS)	
12 - 15	25 (17.9)
8 -12	76 (54.2)
<12	39 (27.9)

Presenting vital signs

Systolic blood pressure (mmHg) 110.77 \pm 22.56

Pulse rate (/minute) 95.48 \pm 23.23

Respiratory rate (/minute) 17.93 \pm 5.33

O2 saturation (%) 88.66 \pm 10.70

Data are presented as mean \pm standard deviation or frequency (%). ESI: emergency severity index;

GCS: Glasgow coma scale.

150 to take account of possible dropout rates. The data were expressed as frequency and percentage or mean \pm standard deviation. The screening performance characteristics of the rapid test for each substance were calculated using MedCalc software and reported with 95% confidence interval (CI).

Table 2 The findings of urine test tape and serum laboratory evaluation for the screening of patients with loss of consciousness regarding 10 important substances

Parameters	Findings		FN	FP	TN	TP
	Standard	Test				
Cocaine	1 (0.7)	2 (1.3)	0 (0.0)	1 (0.7)	148 (99.3)	1 (100.0)
Amphetamine	25 (16.7)	25 (16.7)	4 (16.0)	4 (3.2)	121 (96.8)	21 (84.0)
Methamphetamine	44 (29.3)	43 (28.7)	9 (20.5)	8 (7.5)	98 (92.5)	35 (79.5)
Cannabinoid	3 (2.0)	6 (4.0)	1 (33.3)	4 (2.7)	143 (97.3)	2 (66.7)
Methadone	71 (47.3)	71 (47.3)	6 (8.5)	6 (7.6)	73 (92.4)	65 (91.5)
Morphine	2 (1.3)	2 (1.3)	2 (100.0)	2 (1.4)	146 (98.6)	0 (0.0)
Tramadol	20 (13.3)	23 (15.3)	4 (20.0)	7 (5.4)	123 (94.6)	16 (80.0)
Benzodiazepine	85 (56.7)	87 (58.0)	12 (14.1)	14 (21.5)	51 (78.5)	73 (85.9)
Amitriptyline	3 (2.0)	6 (4.0)	0 (0.0)	3 (2.0)	144 (98.0)	3 (100.0)
Buprenorphine	1 (0.7)	1 (0.7)	1 (100.0)	1 (0.7)	148 (99.3)	0 (0.0)

Standard: serum toxicology evaluation results. Test: the results of urine evaluation with the screening test tape. FN: false negative; FP: false positive; TN: true negative; TP: true positive.

Table 3 The screening performance characteristics of each substance evaluated using the dipstick test

Parameter	Sensitivity	Specificity	PPV	NPV	PLR	NLR
Cocaine	100	99.32	50	100	1	0
	5.46-100.00	95.75-99.96	2.66-97.33	96.84-100.00	0.14-7.09	0-NaN
Amphetamine	84	96.80	84	96.80	5.25	0.03
	63.08-94.74	91.51-98.97	63.08-94.74	91.51-98.97	2.10-13.09	0.01-0.08
Methamphetamine	79.54	92.45	81.39	91.58	4.37	0.09
	64.24-89.67	85.22-96.44	66.08-91.07	84.21-95.83	2.30-8.30	0.04-0.17
Cannabinoid	66.66	97.27	33.33	99.30	0.5	0.0069
	12.53-98.23	92.74-99.12	5.99-75.89	95.61-99.96	0.14-1.77	0.0009-0.04
Methadone	91.54	92.40	91.54	92.40	10.83	0.08
	81.88-96.51	83.60-96.87	81.88-96.51	83.60-96.87	5.02-23.37	0.03-0.17
Morphine	0	98.64	0	98.64	0	0.01
	0-80	94.70-99.76	0-80	94.70-99.76	0-NaN	0.0034-0.05
Tramadol	80	94.61	69.56	96.85	2.28	0.032
	55.73-93.38	88.81-97.62	46.99-85.94	91.94-98.98	1.16-4.48	0.012-0.08
Benzodiazepine	85.88	78.46	83.90	80.95	5.21	0.23
	76.24-92.17	66.19-87.32	74.13-90.61	68.70-89.36	3.19-8.49	0.14-0.39
Amitriptyline	100	97.95	50	100	1	0
	30.99-100	93.68-99.47	13.94-86.05	96.76-100	0.32-3.10	0-NaN
Buprenorphine	0	99.32	0	99.32	0	0.0067
	0-94.53	95.75-99.96	0-94.53	95.75-99.96	0-NaN	0.0009-0.04

All measures are reported with 95% Confidence interval. NaN = Not a number, PPV = Positive predictive value, NPV = Negative predictive value, PLR = Positive likelihood ratio, NLR = Negative likelihood ratio.

3. Results

3.1. Baseline characteristics of studied patients

One hundred fifty patients with the mean age of 46.21 ± 18.59 (range: 16 - 85) years were enrolled in the present study (72.67% male). 125 (83.3%) patients were brought in by the Emergency Medical Services (EMS), and the rest of the patients were transferred to the ED by relatives. 50 (33.3%) pa-

tients arrived in the morning, 53 (35.3%) in the evening, and 47 (31.3%) at night shift. Table 1 indicates the baseline characteristics of participants during the initial ED evaluation. The most frequent underlying disease of patients were cardiovascular in 22 (14.7%), hypertension in 8 (5.3%), and diabetes mellitus in 5 (3.3%) cases. 110 (73.3%) patients had a positive cigarette smoking history, and 39 (26%) were alcohol drinkers.

3.2. Screening performance characteristics of the test

Table 2 shows the findings of urine test tape and serum laboratory evaluation for the screening of patients regarding the 10 studied substances. The most frequent false positive results of the test were related to Benzodiazepine (21.5%), Methamphetamine (7.5%), and Tramadol (5.4%), respectively. Furthermore, the most frequent false negative results of the test were related to Morphine (100.0%), Buprenorphine (100.0%), Methamphetamine (20.5%), and Tramadol (20.0%), respectively. The screening performance characteristics of the test are summarized in table 3. The test tape had the highest sensitivity in detection of Amitriptyline, 100.0% (95% CI: 30.99 – 100.0), Cocaine, 100.0% (95% CI: 5.46 – 100.0), and Methadone, 91.54% (95% CI: 81.88 – 96.51), respectively.

4. Discussion

Based on the findings from the current study, the multi-drug screen test in question demonstrated an overall high specificity and negative predictive value for detecting each substance with a narrow CI in patients with altered mental status. However, regarding sensitivity and positive predictive value, our findings were heterogeneous.

It should be noted that we observed false positive and negative findings concerning almost every substance during the study. In a previous retrospective study, which involved 161 ED patients and aimed to assess the usefulness of immunoassay-based urinary screening test for abused drugs in the ED of a pediatric hospital, employing the screening test changed the management of merely 3.1% of patients (14). In another retrospective study on 323 patients suspected of intoxication presenting to an ED, urine drug screening was carried out in about one-third of them; test results were useful in only two patients and did not impact the management of other patients (6). The present strips can appropriately detect methadone with high sensitivity (91.54%) and specificity (92.40%). A study conducted in 2010 indicated that diphenhydramine, a well-known cutting agent, can give rise to false positive methadone results (15). Fluoroquinolones and verapamil can also cause the same issue (16). Tramadol, another synthetic opioid, has become a widely abused notorious drug throughout the world. Of note, Tramadol toxicity can manifest as seizure, which could increase the importance of screening tests in these patients. As can be seen, the strip can detect tramadol with a sensitivity and specificity of 80% and 94.61%, respectively. Furthermore, both amphetamine and methamphetamine can be identified with fair sensitivity and high specificity. Ephedrine, pseudoephedrine, and bupropion can interfere with immunoassay-based amphetamine screening and produce false positive results (17). All in all, the interpretation of screening assays in the latter category is prominently complicated. The high lipophilicity of cannabis contributes to protracted excretion, especially in chronic users. False negative cannabinoid immunoassay

due to the manipulation of urine by adding some over-the-counter eye drops has been elucidated (18). In our study, the sensitivity of detecting cannabinoids turned out to be 66.66%. We found that the strip test has significant false positive and false negative results for determining the presence of benzodiazepines. Of note, several benzodiazepines, including alprazolam and lorazepam, are excreted in the urine as a conjugated metabolite, which can remain undetected by immunoassay-based tools (19). On the other hand, some commonly prescribed drugs such as sertraline can induce a false positive test (20). Even though we could not find a previous study on the present drug screening tool in the ED setting, the clinical utility of such a screening method in the ED setting seems to be trivial due to remarkable false positive and negative results. Thus, almost always, the result is meant to be presumptive in screening tests and requires time-consuming confirmatory testing. In a nutshell, urinary drug screening strips appear to be inapplicable to ED decision-making due to a possibility of falling into treacherous pitfalls.

5. Limitations

It is noteworthy that our study was a cross-sectional study. In addition, a limited number of patients were enrolled.

6. Conclusion

The current study reveals that employing a urinary strip test in the setting of ED for detecting drug intoxication can lead to significant false positive and negative results. Therefore, relying on a urine drug screen to determine the underlying etiology of LOC should be done with caution.

7. Declarations

7.1. Acknowledgment

We would like to thank all of the nursing and laboratory staff of the emergency departments of Loghman Hakim and Shohadaye Tajrish Hospitals for their cooperation throughout the study.

7.2. Authors' contributions

All authors met the criteria for authorship contribution based on the recommendations of international committee of medical journal editors.

7.3. Conflict of interest

The authors hereby declare that there is no conflict of interest regarding the present study.

7.4. Funding

This study was supported by Men's Health and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

References

- Kanich W, Brady WJ, Huff JS, Perron AD, Holstege C, Lindbeck G, et al. Altered mental status: evaluation and etiology in the ED. *Am J Emerg Med.* 2002;20(7):613-7.
- Völk S, Koedel U, Pfister HW, Schwankhart R, Op den Winkel M, Mühlbauer K, et al. Impaired Consciousness in the Emergency Department. *Eur Neurol.* 2018;80(3-4):179-86.
- Safari S, Khasraghi ZS, Chegeni MA, Ghabousian A, Amini A. The ability of Canadian Syncope risk score in differentiating cardiogenic and non-cardiogenic syncope; a cross-sectional study. *Am J Emerg Med.* 2021;50:675-8.
- Ala A, Vahdati SS, Maroufi P, Hafezan S, Ansari N, Ghabousian A. Philadelphia versus Miami-J cervical collar's impact on pulmonary function. *Am J Emerg Med.* 2021;43:59-61.
- Forsberg S, Höjer J, Enander C, Ludwigs U. Coma and impaired consciousness in the emergency room: characteristics of poisoning versus other causes. *Emerg Med J.* 2009;26(2):100-2.
- Bahji A, Hargreaves T, Finch S. Assessing the utility of drug screening in the emergency: a short report. *BMJ Open Qual.* 2018;7(4):e000414.
- Jones AL, Rankin JA, Then KL. Drug Overdose, Loss of Consciousness, and Compartment Syndrome: A Life-Threatening Combination. *J Emerg Nurs.* 2020;46(3):294-301.
- Sivilotti ML. Flumazenil, naloxone and the 'coma cocktail'. *Br J Clin Pharmacol.* 2016;81(3):428-36.
- Cooksley T, Rose S, Holland M. A systematic approach to the unconscious patient. *Clin Med (Lond).* 2018;18(1):88-92.
- Perrone J, De Roos F, Jayaraman S, Hollander JE. Drug screening versus history in detection of substance use in ED psychiatric patients. *Am J Emerg Med.* 2001;19(1):49-51.
- Fa A-M, Am A, Ar R, editors. Efficiency Evaluation of Urine Collection Vessels with Impeded Urine Adulteration/Substance of Abuse (SOA) Rapid Detection Test Strips 2017.
- Stellpflug SJ, Cole JB, Greller HA. Urine Drug Screens in the Emergency Department: The Best Test May Be No Test at All. *J Emerg Nurs.* 2020;46(6):923-31.
- Moeller KE, Kissack JC, Atayee RS, Lee KC. Clinical Interpretation of Urine Drug Tests: What Clinicians Need to Know About Urine Drug Screens. *Mayo Clin Proc.* 2017;92(5):774-96.
- Ferrer Bosch N, Martínez Sánchez L, Trenchs Sainz de la Maza V, Velasco Rodríguez J, García González E, Luaces Cubells C. [Use of urine drug screening in the emergency department of a paediatric hospital]. *An Pediatr (Engl Ed).* 2018;88(1):19-23.
- Rogers SC, Pruitt CW, Crouch DJ, Caravati EM. Rapid urine drug screens: diphenhydramine and methadone cross-reactivity. *Pediatr Emerg Care.* 2010;26(9):665-6.
- Algren DA, Christian MR. Buyer Beware: Pitfalls in Toxicology Laboratory Testing. *Mo Med.* 2015;112(3):206-10.
- Stout PR, Klette KL, Horn CK. Evaluation of ephedrine, pseudoephedrine and phenylpropanolamine concentrations in human urine samples and a comparison of the specificity of DRI amphetamines and Abuscreen online (KIMS) amphetamines screening immunoassays. *J Forensic Sci.* 2004;49(1):160-4.
- Cone EJ, Bigelow GE, Herrmann ES, Mitchell JM, LoDico C, Flegel R, et al. Non-smoker exposure to secondhand cannabis smoke. I. Urine screening and confirmation results. *J Anal Toxicol.* 2015;39(1):1-12.
- Valentine JL, Middleton R, Sparks C. Identification of urinary benzodiazepines and their metabolites: comparison of automated HPLC and GC-MS after immunoassay screening of clinical specimens. *J Anal Toxicol.* 1996;20(6):416-24.
- Nasky KM, Cowan GL, Knittel DR. False-Positive Urine Screening for Benzodiazepines: An Association with Sertraline?: A Two-year Retrospective Chart Analysis. *Psychiatry (Edgmont).* 2009;6(7):36-9.