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【 ORIGINAL ARTICLE 】

Triage DOA® versus INSTANT-VIEW M-1® in Urinary Drug Screening for Acute Drug Poisoning: A Prospective Cross-sectional Study

Aoi Fujikawa[1], Sachiko Ohde[2], Norio Otani[1] and Shinichi Ishimatsu[1]

Abstract:

Objective In the management of patients with suspected acute drug poisoning, a screening test using the patient's urine is usually performed. The Triage DOA® and INSTANT-VIEW M-1® kits are two commonly used point-of-care screening kits in Japan. However, the relationship between the results of these screening kits and the blood concentration of the poisoning drug is not clear. In this study, we evaluated which kit is more useful for acute drug poisoning screening based on a comparison of their results with the results of a serum drug analysis.

Methods This prospective cross-sectional study investigated all patients with acute drug poisoning admitted to a general hospital in Tokyo, Japan, over a nine-month period. The Triage DOA® and INSTANT-VIEW M-1® screening kits were used, and a qualitative serum analysis was conducted simultaneously in all cases. We compared the kits for use in screening patients with acute drug poisoning and evaluated the utility of the kits.

Results For the 117 patients enrolled in this study, the 2 kits showed different sensitivities to benzodiazepines (Triage®, 78.6%; INSTANT-VIEW®, 90.5%). Both kits showed high sensitivity to barbiturates (Triage®, 87.0%; INSTANT-VIEW®, 91.3%) but low sensitivity to tricyclic antidepressants (Triage®, 25.0%; INSTANT-VIEW®, 45.8%).

Conclusion Because the sensitivity varies depending on the kind of drug, it is difficult to discuss the superiority of these kits. However, this study compared the results of two types of urinary drug screening kits with the results of qualitative analysis of drugs in serum as a gold standard, providing important reference data.

Key words: Triage DOA®, INSTANT-VIEW M-1®, acute drug poisoning, screening test

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Introduction

When patients suspected of having acute drug poisoning are encountered, the poisoning drug is usually identified by an analysis of a urine sample with a drug screening kit. At the same time, a serum sample is taken to measure the blood concentration of the drug. A urine screening test is the standard method of drug screening worldwide because it is simple to administer (1-3). The Triage DOA® and INSTANT-VIEW M-1® kits have recently become the most widely used drug screening kits in Japan (4-7).

Since the Triage DOA® kit (Sysmex, Kobe, Japan) was released in Japan in 1994, it has become widely used due to its low price, convenience, and large number of detectable drug groups (5, 6). A previous study of its clinical utility (8) using the quantitative analysis results of drugs in blood as a gold standard concluded that this kit is useful as a primary screening test for emergency initial treatment due to its sensitivity, specificity, positive predictive value, and negative

[1]St. Luke's International Hospital Emergency & Critical Care Medicine, Japan and [2]Center for Clinical Epidemiology, Graduate School of Public Health Planning Office, St. Luke's International University, Omura Susumu & Mieko Memorial, St. Luke's Center for Clinical Academia, Japan
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Correspondence to Dr. Aoi Fujikawa, aoifjkw@luke.ac.jp

Table 1. Seropositive Items Examined in Patients with Suspected Acute Drug Poisoning.

Benzodiazepines	Alprazolam / Bromazepam / Brotizolam / Chlordiazepoxide / Clobazam / Clonazepam / Demoxepam / Diazepam / Estazolam / Etizolam / Flunitrazepam / Flurazepam / Lorazepam / Nitrazepam / Nordiazepam / Oxazepam / Temazepam / Triazolam / D5-diazepam
Barbiturates	Amobarbital / Pentobarbital / Phenobarbital / Phenobarbital metabolite
Tricyclic antidepressants	Alimemazine / Amitriptyline / Amoxapine / Clomipramine / Desipramine / Imipramine / Nortriptyline / Trimipramine / Amitriptyline-M-H_2O / Clomipramine-M (HO-) / Clomipramine-M (bis-nor-) / Clomipramine-M (nor-) / Clomipramine-M (bis-nor-HO-) / Nordesipramine / N-Desmethylclomipramine
Amphetamines	MDMA / Phenethylamine / MDA / Methamphetamine
Cocaine	Cocaine
Cannabis	Cannabinol

predictive value.

The result of Triage DOA® merely determines whether a sample is positive or negative based on the cut-off value of the urinary drug concentration but cannot readily detect poisoning (5). Regarding the cut-off value, it has been reported that Triage DOA® detects benzodiazepines (BZOs) and tricyclic antidepressants (TCAs) at concentrations lower than the cut-off levels due to the presence of metabolites of BZOs and TCAs (9). Therefore, emergency physicians must remember that the screening kit is not a panacea.

The cross-reactivity of methamphetamine and chlorpromazine metabolites can cause a false-negative Triage DOA® reaction for amphetamines (10). The influence of the interactions among multiple kinds of drugs on the results of the kit cannot be ignored in multidrug poisoning patients.

Since the INSTANT-VIEW M-1® (Fujirebio, Tokyo, Japan) was released in Japan in 2010, the number of facilities using it has rapidly increased. One of the main reasons for its popularity is that decision-making is simpler than with Triage DOA® (11). However, in a study comparing Triage DOA® and INSTANT-VIEW M-1® judgment results based on urinary drug concentrations, it was difficult to determine kit superiority (7).

No reports have examined which kit is more useful at clinical sites in terms of the accuracy of drug concentration in the blood and the results of the kit. The relationship between the results of these screening kits and the serum analysis of the poisoning drug is also not clear. Accordingly, we compared the results of the two kits to determine which kit is more useful for drug screening.

Materials and Methods

This study followed a prospective cross-sectional design. It was conducted between March 29, 2012, and December 31, 2012, at the Critical Care Center of St. Luke's International Hospital, Japan. The center received 7,960 ambulance patients and 36,421 walk-in patients in 2012, approximately 0.4% of whom (172) were admitted because of acute drug poisoning. We excluded patients <15 years of age, hemodialysis patients (patients without their own urine), and pregnant women. In accordance with the provisions of the hospital, informed consent was obtained from all patients for their participation in this study.

We carried out drug screening for each patient using the two screening kits and collected blood for a serum analysis at the same time. The screening kits used were Triage DOA® (Sysmex) and INSTANT-VIEW M-1®. The Materials Science Technology Promotion Foundation conducted a qualitative drug analysis of the serum samples using gas chromatography. The drug categories detectable by both kits were BZO, barbiturates (BAR), TCAs, amphetamines (AMP), cocaine (COC), and cannabis (THC). Each seropositive item is shown in Table 1.

We extracted the patients' basic data and laboratory data from our hospital records and supplemented these data with the results of a qualitative serum drug analysis and the results of both kits. We then calculated the sensitivity and specificity of the drugs detected by the kits.

We also performed a subgroup analysis in which we divided patients into two subgroups-those who had taken only one kind of drug and those who had taken multiple drugs-based on medical interviews. We then calculated the sensitivity and specificity of the drugs detected by the above-mentioned kits.

Furthermore, we examined the agreement rate between the screening kit and serum results for each drug between the two subgroups. The p-value was calculated using the chi-square test for each drug; a p value <0.05 was considered statistically significant.

The protocol for this research project was approved by a suitably constituted Ethics Committee of St. Luke's International Hospital, and it conforms to the provisions of the Declaration of Helsinki. Informed consent was obtained from the subjects or guardians. The authors declare that they have no competing interests and no reciprocity agreement with the Materials Science Technology Promotion Foundation that conducted the qualitative drug analysis.

Results

During the 9-month study period, we enrolled 117 cases

Table 2. Demographics and Patients' Characteristics.

Item	Case
Average age	39.0±19.0 years
Sex	
Male	38 (32.5%)
Female	79 (67.5%)
History of psychiatric illness	
Positive	88 (75.2%)
Negative	29 (24.3%)
Impairment of consciousness (Glasgow Coma Scale)	
10-15	77 (65.8%)
3-9	40 (34.2%)
Numbers of kinds of drugs of abuse on medical interview	
One kind of drug	19 (16.2%)
More than one kind of drug or Vegetamin®	69 (59.0%)
Includes over-the-counter drug	15 (12.8%)
Quasi-legal herbs	4 (3.4%)
Household detergent	2 (1.7%)
Unknown	8 (6.8%)

Because Vegetamin® is a mixture, it was treated as a multiple drug.

of acute drug poisoning (79 women, 38 men; mean age, 39.0 years; age range, 15-91 years) and analyzed their urine samples. Patients' backgrounds are shown in Table 2. Among the patients, 77 (65.8%) had a Glasgow Coma Scale (GCS) score of ≥10 when transported to our hospital, and 40 (34.2%) had a GCS score of ≤9. In the medication interview, conducted with the patient, family, or emergency team to obtain information on medication contents, 19 patients (16.2%) took only 1 kind of drug, and 69 (59.0%) took ≥2 drugs; we defined the former as the single-drug user group and the latter as the multiple-drug user group. The multiple-drug user group included patients who took only Vegetamin®. Because Vegetamin® is a mixture, it was treated as multiple drugs. Out of all investigated patients, 15 (12.8%) were simultaneously taking over-the-counter (OTC) drugs, 4 (3.4%) consumed quasi-legal herbs (e.g. synthetic cannabinoids), 2 (1.7%) had ingested domestic detergent, and 8 (6.8%) had unknown medication contents.

Table 3 shows the specificity and sensitivity of Triage DOA® and INSTANT-VIEW M-1® for each category of drug. BZO sensitivity was 78.6% with Triage DOA® and 90.5% with INSTANT-VIEW M-1®. BAR sensitivity was 87.0% with Triage DOA® and 91.3% with INSTANT-VIEW M-1®. The specificity of both kits was low for BZO (Triage DOA®, 48.0%; INSTANT-VIEW M-1®, 41.3%) but high for BAR (Triage DOA®, 95.7%; INSTANT-VIEW M-1®, 98.9%). For TCAs, the sensitivities of the Triage DOA® and INSTANT-VIEW M-1® kits were low at 25.0% and 45.8%, respectively. Because no patient showed serum positivity for THC or AMP, the sensitivity of the kits to these drugs could not be calculated. In addition, no patient was shown to be positive for COC according to either a kit or serum analysis, and the specificity and sensitivity could not be calculated.

More than half of the patients were taking more than one

Table 3. Sensitivity and Specificity of the Triage DOA® and INSTANT-VIEW M-1® Kits for Each Kind of Drug Tested.

Drug	Serum Positive	Serum Negative	Triage DOA®					INSTANT-VIEW M-1®				
			True Positive	True Negative	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	True Positive	True Negative	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV
BZO	42	75	33	36	78.6% (63.2-89.7%)	48.0% (36.3-59.8%)	45.8%	80.0%	38	31	90.5% (77.4-97.3%)	41.3% (30.1-53.3%)	46.3%	88.6%
BAR	23	94	20	90	87.0% (66.4-97.2%)	95.7% (89.5-98.8%)	83.3%	96.8%	21	93	91.3% (72.0-98.9%)	98.9% (94.2-100%)	95.5%	97.9%
TCAs	24	93	6	91	25.0% (9.8-46.7%)	97.8% (92.4-99.7%)	75.0%	83.5%	11	84	45.8% (25.6-67.2%)	90.3% (82.4-95.5%)	55.0%	86.6%
THC	0	117	0	115	N.D.	98.3%	N.D.	N.D.	0	113	N.D.	96.6%	N.D.	N.D.
AMP	0	117	0	116	N.D.	99.1%	N.D.	N.D.	0	116	N.D.	99.1%	N.D.	N.D.

AMP: amphetamines, BAR: barbiturates, BZO: benzodiazepines, TCAs: tricyclic antidepressants, THC: cannabis, N.D.: not detected, PPV: positive predictive value, NPV: negative predictive value, CI: confidence interval

drug. In consideration of the influence of cross-reactivity between drugs on the results of the kits, the sample was divided into two groups-a single-drug user group and a multiple-drug user group-and the sensitivity and specificity of the two kits were compared (Table 4). In total, 88 patients were analyzed, after the exclusion of patients who had taken OTC drugs or consumed quasi-legal herbs and household chemicals.

In the single-drug user group (19 patients), the BZO sensitivity was 60.0% with Triage DOA® and 80.0% with INSTANT-VIEW M-1®, and the specificity was 35.7% with Triage DOA® and 50.0% with INSTANT-VIEW M-1®. The BAR sensitivity was 100% with both Triage DOA® and INSTANT-VIEW M-1®, and the specificity was 83.3% with Triage DOA® and 94.4% with INSTANT-VIEW M-1®. The TCA sensitivity and specificity could not be calculated because no patient was seropositive for TCAs in the single-drug user group.

In the multiple-drug user group (69 patients), the BZO sensitivity exceeded 90% in both kits, and the BAR sensitivity was 94.7% in both kits. However, with respect to TCAs, the sensitivity was 25.0% with the Triage DOA® and 45.8% with INSTANT-VIEW M-1®. Both TCA sensitivities were low, and this result was similar to the TCA sensitivity result obtained in all patients.

In addition, we examined whether or not there was a difference between the drug user groups in terms of the agreement rate of the kit result and the serum result for each drug (Table 5). With Triage DOA®, the agreement rate of TCAs was 100% in the single-drug user group but 72.5% in the multiple-drug user group (p=0.009). With INSTANT-VIEW M-1®, the agreement rate of TCAs was 100% in the single-drug user group but 71.0% in the multiple-drug user group (p=0.005). In both screening kits, the agreement rate was significantly lower in the multiple-drug user group than in the single-drug user group. The agreement rate of BAR was 84.2% in the single-drug user group but 98.6% in the multiple-drug user group (p=0.030) with the Triage DOA®, which thus indicated a significant difference. While there was no significant difference in the agreement rate, the agreement rate was 94.7% for the single-drug user group and 98.6% for the multiple-drug user group with INSTANT-VIEW M-1®. Regarding BZO, regardless of the number of drugs, the agreement rate was around 50% in both kits, and no significant difference was found.

Discussion

Overall, our finding that both kits have high specificity and sensitivity to BAR and high sensitivity to BZO shows that they are useful in the clinical setting. However, the lower specificity of the kits to BZO might reflect a false-positive reaction with drugs other than BZO, indicating a cross-reaction. The low specificity of the kits to BZO is consistent with the results of previous studies (7, 8). The relatively low sensitivity of the Triage DOA® to TCAs may be for one of the following reasons: the concentration of drug detected in the serum analysis might be lower than the detection limit of the kit; urinary protein or highly viscous material might react abnormally with the drug; or the metabolites of the drug in urine might not react correctly with the kit.

Given that sensitivity is more important than specificity in the clinical setting, INSTANT-VIEW M-1® may be more useful than Triage DOA® for screening because of its simpler method and higher sensitivity. In this study, although the statistical evidence was unclear because there was an insufficient number of cases, the finding that BZO and BAR sensitivity was higher with INSTANT-VIEW M-1® than with Triage DOA® will be an important point to consider in future studies.

In the emergency room, many patients with acute drug poisoning have taken more than one drug. Indeed, 59.0% of patients in the present study had consumed multiple drugs. Therefore, when a urine screening kit is used at a clinical site, it is necessary to fully consider the influence of cross-reactivity between drugs. For this reason, we examined each drug and both kit results in single-drug and multiple-drug user groups.

Unfortunately, the sample size was insufficient for an adequately powered statistical analysis, but the results still revealed that BZO showed higher sensitivity in the multiple-drug user group than in the single-drug user group. This result suggests that false negatives decrease as the number of different drug types increases, which is a favorable result when screening acute drug poisoning patients. For BAR, regardless of whether single or multiple drugs had been taken, both kits showed high sensitivity (single-drug user group: Triage DOA®, 100%; INSTANT-VIEW M-1®, 100%; multiple-drug user group: Triage DOA®, 94.7%; INSTANT-VIEW M-1®, 94.7%). For Triage DOA®, BAR is said to give the most reliable results (5), but our results suggest that this could also be said about INSTANT-VIEW M-1®.

We obtained novel findings concerning the agreement rate. In this study, because there were no seropositive cases of TCAs in the single-drug user group, no generalizable conclusions can be made, but the agreement rate of TCAs was significantly lower in the multiple-drug user group than in the single-drug user group with both screening kits.

To interpret the results of the drug screening kits in multidrug patients, it is necessary to consider how reliable the results are for each drug. However, although this result seems to be a useful finding for evaluating the interaction of drugs, the rate of inconsistency between the drug information obtained from patients, their relatives, and other sources and the serum analysis result was 7.4% in a previous study (6). This is a limitation of any comparisons of single-drug and multiple-drug users that rely on medical interviews.

Regarding kit handling, INSTANT-VIEW M-1® is more convenient than Triage DOA® due to its ease-of-use. The single-step operation of uniformly dropping a patient's urine

Table 4. **Sensitivity and Specificity of the Triage DOA® and INSTANT-VIEW M-1® Kits for Each Kind of Drug Tested (Focusing on the Number of Drugs).**

Drug	Serum Positive	Serum Negative	Triage DOA®						INSTANT-VIEW M-1®					
			True Positive	True Negative	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	True Positive	True Negative	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV
Single-drug user group (19 patients)														
BZO	5	14	3	5	60.0% (14.7-94.7%)	35.7% (12.8-64.9%)	25.0%	71.4%	4	7	80.0% (28.4-99.5%)	50.0% (23.0-77.0%)	36.4%	87.5%
BAR	1	18	1	15	100% (N.D.)	83.3% (58.6-96.4%)	50.0%	100%	1	17	100% (N.D.)	94.4% (72.7-99.9%)	50.0%	100%
TCAs	0	19	0	19	- (N.D.)	100% (N.D.)	-	100%	0	19	- (N.D.)	100% (N.D.)	-	100%
Multiple-drug user group (69 patients)														
BZO	30	39	27	12	90.0% (73.5-97.9%)	30.8% (52.4-83.0%)	50.0%	80.0%	28	8	93.3% (77.9-99.2%)	20.5% (63.5-90.7%)	47.5%	80.0%
BAR	19	50	18	50	94.7% (74.0-99.9%)	100% (N.D.)	100%	98.0%	18	50	94.7% (74.0-99.9%)	100% (N.D.)	100%	98.0%
TCAs	24	45	6	44	25.0% (9.8-46.7%)	97.8% (88.2-99.9%)	85.7%	71.0%	11	38	45.8% (25.6-67.2%)	84.4% (70.5-93.5%)	61.1%	74.5%

Single-drug user group: patients who took one kind of drug.

Multiple-drug user group: patients who took more than one kind of drug or who took Vegetamin®. Because Vegetamin®is a mixture, it was treated as a multiple drug.

Patients who took over-the-counter drugs, quasi-legal herbs, or household detergent were excluded from this table. Patients whose drugs of abuse were unknown were also excluded.

BAR: barbiturates, BZO: benzodiazepines, TCAs: tricyclic antidepressants, N.D.: not detected, PPV: positive predictive value, NPV: negative predictive value, CI: confidence interval

onto the sample window and making a judgment is simple important in understaffed hospital emergency rooms. In this with INSTANT-VIEW M-1®, and this simplicity is critically regard, it can be said that INSTANT-VIEW M-1® is the su-

Table 5. Agreement Rate between Screening Kit Results and Serum Results for Each Drug (Comparison of Single-drug Users and Multiple-drug Users).

Drug		Single-drug users n=19 (95% CI)	Multiple-drug users n=69 (95% CI)	p value
BZO	Triage DOA®	42.1% (20.3-66.5%)	56.5% (44.0-68.4%)	0.306
	INSTANT-VIEW M-1®	57.9% (33.5-79.7%)	52.2% (39.8-64.4%)	0.796
BAR	Triage DOA®	84.2% (60.4-96.6%)	98.6% (92.2-100%)	0.030
	INSTANT-VIEW M-1®	94.7% (74.0-99.9%)	98.6% (92.2-100%)	0.387
TCAs	Triage DOA®	100.0% (N.D.)	72.5% (60.4-82.5%)	0.009
	INSTANT-VIEW M-1®	100.0% (N.D.)	71.0% (58.8-81.3%)	0.005

BAR: barbiturates, BZO: benzodiazepines, TCAs: tricyclic antidepressants, CI: confidence interval

perior choice.

The present study has several limitations. First, in this single-center study, the majority of patients had blood test results within the normal range, but different results might be obtained for patients with different backgrounds. Second, because most of the patients took multiple drugs, we were unable to exclude the possibility that cross-reactions of the drugs influenced the results of the kits. Third, we performed only qualitative analyses drugs in serum and did not consider the blood concentration (i.e., the quantitative evaluation of serum drugs was not performed). Finally, we did not consider the prices of the kits because we were more interested in the performance of the screening kits than their cost.

In conclusion, we evaluated which drug screening kit was more useful for screening based on serum drug analysis results. In the clinical setting, both Triage DOA® and INSTANT-VIEW M-1® can be used to screen for drugs of abuse given their sensitivity to the poisoning drugs described here. However, as noted previously (7), it is still difficult to definitively determine the superiority of kits because their sensitivities vary depending on the drug being detected. However, to our knowledge, this study is the first to compare the results of two types of urinary drug screening kits with the qualitative analysis of drugs in serum as a gold standard. We hope that the results will be useful as important reference data in the future.

The authors state that they have no Conflict of Interest (COI).

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