Interpreting Tricyclic Antidepressant Measurements in Urine in an Emergency Department Setting: Comparison of Two Qualitative Point-of-Care Urine Tricyclic Antidepressant Drug Immunoassays with Quantitative Serum Chromatographic Analysis

Stacy E.F. Melanson[1], Elizabeth Lee Lewandrowski[2], David A. Griggs[2], and James G. Flood[2,*]

[1]Division of Clinical Laboratories, Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts and [2]Department of Pathology, Massachusetts General Hospital and Harvard Medical School, 55 Fruit Street, Boston, Massachusetts 02114

Abstract

Patients taking tricyclic antidepressants (TCA) can experience toxicity or severe side effects. As a rapid and less technically demanding alternative to quantitative serum analysis, most laboratories offer qualitative immunoassays to assist in the evaluation of a suspected TCA overdose. However, the relationship between quantitative serum and qualitative urine levels of TCA-related compounds and their metabolites has not been comprehensively studied. Serum high-performance liquid chromatography results were compared to the qualitative urine results using the Syva Rapid Test and the Biosite Triage. Serum concentrations of amitriptyline, desipramine, doxepin, imipramine, and nortriptyline ranging from subtherapeutic to toxic triggered a positive response on both urine immunoassay devices. On the other hand, neither immunoassay uniformly detected clomipramine, even at serum levels greater than the therapeutic range. False positives due to cyclobenzaprine were more common with the Biosite assay. For virtually all positive urine TCA findings, it was not possible to determine whether the positive results corresponded to subtherapeutic, therapeutic, supratherapeutic, or toxic serum concentrations. Because urine immunoassays are the only option for many laboratories analyzing specimens for TCAs (especially in an emergency setting), clinicians must understand the limitations and interpret results in conjunction with clinical findings and/or quantitation of serum levels.

Introduction

Tricyclic antidepressants (TCA) are commonly used to treat depression, anxiety disorders, eating disorders, attention deficit hyperactivity disorder, enuresis in children, and as an adjunct for neuropathic pain. Amitripyline, nortripyline, clomipramine, desipramine, imipramine, and doxepin are classified as TCA. Despite their utility in various clinical disorders, compared to other antidepressants, TCAs carry the risk of severe side effects, even in patients taking the recommended dosage. In 2004, over 12,000 overdoses were due to TCAs, 11% of which resulted in serious adverse outcomes or death (1). The clinical presentation of TCA overdose may include anticholinergic effects (dry mouth, blurred vision, constipation, urinary retention, and decreased sweating) and cardiac conduction abnormalities (2–4).

Monitoring quantitative serum levels of TCA can improve therapeutic management, especially in patients with questionable compliance, potential toxicity, or suspected drug-drug interactions. The National Academy of Clinical Biochemistry recommends monitoring the levels of impramine, desipramine, amitriptyline, nortriptyline, and doxepin (3). Clomipramine levels may also be helpful. However, many laboratories do not have the technological expertise or equipment available to provide quantitative serum TCA levels. Reference laboratories can be utilized when assessing compliance or drug-drug interactions; however, more rapid turnaround times are needed in patients with signs and symptoms of toxicity.

In cases of suspected TCA toxicity, an on-site laboratory is preferable. Urine immunoassays that provide rapid qualitative results can be implemented either in the laboratory or at the point-of-care (POC) in most institutions. Studies have compared the available urine immunoassays, and the agreement is usually acceptable (5–9). However, immunoassays for TCA have several limitations, including false-positive results and poor specificity (6,9–12). For evaluating potential toxicity, an optimal cutoff, which alerts the physician to TCA toxicity, not

* Author to whom correspondence should be addressed: James G. Flood, Department of Pathology, Massachusetts General Hospital, 55 Fruit Street, GRJ 5, Boston, MA 02114. E-mail: jflood@partners.org.

therapeutic levels, regardless of which TCA is present, would be ideal (5). This may not be possible, considering the range of specificities of the current immunoassays and the fact that patients can experience serious side effects even at therapeutic concentrations.

Because of the limitations of urine immunoassays, laboratorians and physicians may need assistance with result interpretation, especially when determining how a qualitative urine result correlates with quantitative serum concentrations. Although several studies have utilized serum high-performance liquid chromatography (HPLC) or thin-layer chromatography to verify discordant results between immunoassays, to our knowledge, no studies have examined how qualitative urine results correlate with quantitative serum results for an individual TCA. In this study, a serum HPLC analysis is performed in conjunction with two different POC urine immunoassay devices in order to (*i*) determine which TCAs at what range of serum concentrations (subtherapeutic to toxic) will produce a positive urine screen and (*ii*) examine the utility of immunoassays for urine TCA in the evaluation of potential toxicity.

Methods

Fifty-two consecutive emergency room patients from two time periods, January 3 to May 24, 2005, and September 14 to November 30, 2006, having a positive serum for a TCA or the muscle relaxant cyclobenzaprine and a simultaneously collected urine sample (i.e., within 15 min of the blood draw) were included in the study. Patients taking cyclobenzaprine were included because cyclobenzaprine is a known interferant in immunoassays designed to detect TCAs. Blood and urine samples from emergency department patients are sent to the laboratory via a pneumatic tube transportation system and processed immediately upon receipt by the laboratory. Upon completion of analysis (usually 1–3 h), all urine and serum samples are stored frozen at –20°C.

Quantitative serum chromatographic analysis was performed on all specimens using liquid chromatography with photodiode-array detection (LC–PDA) (12). The detection limits for TCAs and cyclobenzaprine using LC–PDA were 5 ng/mL for amitriptyline, clomipramine, cyclobenzaprine, doxepin, imipramine, norclomipramine, and nortriptyline and 10 ng/mL for desipramine. The therapeutic and toxic ranges for these drugs are listed in Table I.

The Syva Rapid Test d.a.u. TCA Test (Syva, San Jose, CA) is a one-step immunochromatographic test for the rapid, qualitative detection of TCA in human urine. It is a visually read POC test with the separation of positive from negative results set by a 1000 ng/mL nortriptyline cutoff calibrator. Reactivities of the test toward other TCA and metabolites are listed in Table II. If no red color bar is observed 5 min after the application of a patient's urine sample, the sample is considered a presumptive positive for TCA.

The Biosite Triage (Biosite, San Diego, CA) TOX Drug Screen POC assay is a two-step immunochemical technique that uses a monoclonal antibody system in a competitive binding mode. The fluorescence developed when a target drug and/or metabolite is present in a urine sample is measured by a Triage Meter Plus. The meter decides if the fluorescence exceeds that of the cutoff calibrator (1000 ng/mL of desipramine). If yes, it reports the urine as being positive for a TCA. If the fluorescence is less than the calibrator, the meter reports the urine to be negative. Reactivities of the test toward other TCAs and metabolites are listed in Table II. As stated by Biosite, cyclobenzaprine is a known interferant with the TCA drug of abuse assay.

After serum analysis, all corresponding urines were collected, stored frozen at –20°C, and later assayed using the two POC immunoassay devices. Both assays were performed according to manufacturer instructions by trained technologists blinded to the serum results. The quantitative serum HPLC re-

Table I. Therapeutic and Toxic Concentrations of Tricyclic Antidepressants (3)

Drug Name	Therapeutic Range (ng/mL)	Toxic Range (ng/mL)
Amitriptyline*	80–250	> 450
Clomipramine	70–200	> 400
Desipramine	125–300	> 450
Doxepin	150–250	> 450
Imipramine*	150–250	> 450
Nortriptyline	50–150	> 450
Cyclobenzaprine	10–40	> 260

* Includes levels of parent compound and metabolite.

Table II. Cross-Reactivity of Urine Immunoassays to Individual Tricyclic Antidepressants

Compound	Concentration (ng/mL) Required to Yield a Positive Result in Package Insert	
	Biosite Triage	Syva Rapid Test
Amitriptyline	750	1000
Amitriptyline metabolite (d,l-E-10-hydroxy-amitriptyline)	250	Not Listed
Clomipramine	12,500	7500
Clomipramine metabolite (Norclomipramine)	75,000	50,000
Cyclobenzaprine	1900	1500
Desipramine	1000	1000
Dothiepin	1000	125
Doxepin	1300	1000
Doxepin metabolite (Nordoxepin)	1500	1000
Imipramine	600	850
Nortriptyline	1100	1000
Nortriptyline metabolite (± E-10-hydroxylated)	750	Not Listed
Nortripyline metabolite (± Z-10-hydroxylated)	5000	Not Listed
Protriptyline	3300	400
Trimipramine	3000	1500

sults were compared to the qualitative results on the Syva Rapid Test and the Biosite Triage assay. In selected specimens quantitative urine chromatographic analysis was performed identical to that described for serum, and urinary creatinine levels were measured using the Roche Hitachi 911 analyzer and Roche reagents (Roche Diagnostics, Indianapolis, IN).

Results

The therapeutic ranges and toxic ranges are not well-defined for all TCAs, but the ranges listed in Table I are generally accepted as guidelines for therapeutic drug monitoring (4). Amitriptyline and imipramine are metabolized to their respective active metabolites, nortriptyline and desipramine. Therapeutic ranges for these compounds are usually defined by the sum of the parent compound and its active metabolite.

The 52 consecutive emergency room patients had a different TCA and/or cyclobenzaprine in their serum at a range of concentrations. This study included patients with subtherapeutic serum concentrations of amitriptyline/nortriptyline, clomipramine, doxepin, and imipramine/desipramine; therapeutic serum concentrations of amitriptyline/nortriptyline, clomipramine, cyclobenzaprine, and nortriptyline; supratherapeutic serum concentrations of amitriptyline/nortriptyline, cyclobenzaprine, and nortriptyline; and toxic serum concentrations of amitriptyline/nortriptyline (Table III). Five patients had more than one TCA or a TCA and cyclobenzaprine in their serum.

Amitriptyline/nortriptyline at concentrations ranging from subtherapeutic to toxic triggered a positive result on both the Syva and Biosite devices (Table III). There was one discrepancy between the Syva and the Biosite in a patient with low serum concentrations of amitriptyline (18 ng/mL)/nortriptyline (8 ng/mL), in which the Biosite was positive and the Syva was negative (Table IV). This specimen had a very low urinary creatinine concentration of 11.8 mg/dL and amitriptyline and nortriptyline levels of 20 and 23 ng/mL, respectively.

At subtherapeutic and therapeutic concentrations of clomipramine, Biosite was consistently negative and Syva was positive in 50% of the patients (Table III). Serum clomipramine concentrations of 65 and 168 ng/mL resulted in a positive urine test on the Syva device (Table IV), though concentrations of 58 and 85 ng/mL resulted in a negative urine test. The corresponding urine clomipramine and creatinine concentrations are listed in Table IV. Both cases in which the Syva device was positive had much higher urine concentrations of clomipramine and its metabolite norclomipramine.

Serum doxepin, imipramine/desipramine, and nortriptyline at subtherapeutic and therapeutic levels always were associated with a positive result on both immunoassay devices. One pa-

Table III. Comparison of Serum Tricyclic Antidepressant Levels with Qualitative Urine Drug Screen Results

Analyte	Frequency	Serum Concentration	% Positive Urine (Biosite)	% Positive Urine (Syva)
Amitriptyline/Nortriptyline*	14	Subtherapeutic (< 80 ng/mL)	100	94.7
	8	Therapeutic (80–250 ng/mL)	100	100
	4	Supratherapeutic (251–450 ng/mL)	100	100
	2	Toxic (> 450 ng/mL)	100	100
Clomipramine	2	Subtherapeutic (< 70 ng/mL)	0	50
	2	Therapeutic (70–200 ng/mL)	0	50
Cyclobenzaprine	4	Therapeutic (10–40 ng/mL)	100	25
	1	Supratherapeutic (41–260 ng/mL)	100	100
Doxepin	4	Subtherapeutic (< 150 ng/mL)	100	100
Imipramine/Desipramine*	2	Subtherapeutic (< 150 ng/mL)	100	100
Nortriptyline	2	Therapeutic (50–150 ng/mL)	100	100
	2	Supratherapeutic (151–450 ng/mL)	100	100
Nortriptyline	1	Therapeutic (50–150 ng/mL)	100	100
Imipramine/Desipramine*		Subtherapeutic (< 150 ng/mL)		
Cyclobenzaprine	1	Subtherapeutic (41–260 ng/mL)	100	100
Doxepin		Subtherapeutic (< 150 ng/mL)		
Cyclobenzaprine	1	Therapeutic (10–40 ng/mL)	100	100
Nortriptyline		Supratherapeutic (151–450 ng/mL)		
Cyclobenzaprine	2	Supratherapeutic (41–260 ng/mL)	100	100
Amitriptyline/Nortriptyline*		Therapeutic (80–250 ng/mL)		

* Amitriptyline and imipramine are considered together with their metabolites, nortriptyline and desipramine, respectively.

tient taking a combination of nortriptyline and imipramine/desipramine also had a positive urine result by both devices (Table III).

The muscle relaxant cyclobenzaprine has been reported to cause false-positive results on TCA immunoassays, and some manufacturers state this interference in their package insert. This study showed that both therapeutic and supratherapeutic serum concentrations of cyclobenzaprine were associated with a positive urine result on the Biosite. However, in most cases, therapeutic serum concentrations of cyclobenzaprine did not produce a positive urine result using the Syva device (Table III). Table IV illustrates the three discrepant and two concordant cases including the quantitative serum levels, the urinary creatinine concentrations, and the qualitative urine results. Serum cyclobenzaprine concentrations of 10, 13, and 24 ng/mL were associated with positive urine results using Biosite and negative results using Syva, and serum concentrations of 14 and 74 ng/mL produced a positive urine result on both devices. The case with a cyclobenzaprine concentration of 14 ng/mL had highly concentrated urine as suggested by the creatinine of 467.1 mg/dL. Patients taking a combination of cyclobenzaprine and TCA also triggered a positive urine result.

All positive serum TCA findings (except those due to clomipramine and one due to amitriptyline) were associated with a positive urine TCA using both immunoassays. The sensitivity, specificity, positive predictive value, and negative predictive value of each device was determined according to the HPLC results with a true positive as the presence of any TCA in the serum and a true negative as the presence of cyclobenzaprine only in the serum. Using this criteria, the sensitivity of the Biosite and Syva assays for the detection of urine TCA was 89.6% and 95.7% (Table V). The specificities were 0% for the Biosite assay and 50% for the Syva device. Both assays had a positive predictive value greater than 90%.

Table IV. Selected Urine Drug Screen Results for Tricyclic Antidepressants

Case	Analyte	Serum Concentration	Urine Concentration	Urine Creatinine Concentration	Biosite Urine Result	Syva Urine Result
1	Amitriptyline Nortriptyline	18 ng/mL 8 ng/mL	20 ng/mL 23 ng/mL	11.8 mg/dL	Positive	Negative
2	Clomipramine Norclomipramine	47 ng/mL 154 ng/mL	320 ng/mL 1300 ng/mL	39.1 mg/dL	Negative	Positive
3	Clomipramine Norclomipramine	168 ng/mL 235 ng/mL	390 ng/mL 870 ng/mL	21.6 mg/dL	Negative	Positive
4	Clomipramine Norclomipramine	58 ng/mL 340 ng/mL	< 20 ng/mL 150 ng/mL	53.9 mg/dL	Negative	Negative
5	Clomipramine Norclomipramine	85 ng/mL 45 ng/mL	< 20 ng/mL 40 ng/mL	64.4 mg/dL	Negative	Negative
6	Cyclobenzaprine	10 ng/mL	N/A*	150.5 mg/dL	Positive	Negative
7	Cyclobenzaprine	13 ng/mL	N/A	52.6 mg/dL	Positive	Negative
8	Cyclobenzaprine	24 ng/mL	N/A	113.6 mg/dL	Positive	Negative
9	Cyclobenzaprine	14 ng/mL	N/A	467.1 mg/dL	Positive	Positive
10	Cyclobenzaprine	74 ng/mL	N/A	56.9 mg/dL	Positive	Positive

* N/A = assay not performed on this specimen.

Table V. Performance Characteristics of the Biosite Triage and Syva Rapid Test Urine TCA Immunoassays Using Serum HPLC as the Definitive Result

Assay	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value	Negative Predictive Value
Biosite Triage	89.6 (77.3–96.5)	0.0 (0.0–60.2)	91.5	0.0
Syva Rapid Test	95.7 (85.2–99.5)	50.0 (11.8–88.2)	93.6	60.0

Discussion

TCAs including amitriptyline, clomipramine, desipramine, doxepin, imipramine, and nortriptyline are routinely prescribed for depression and other psychiatric or pain-related disorders. Because of the high risk of serious side effects and drug-drug interactions, drug levels are frequently monitored in patients on these medications. In addition, TCA are commonly a culprit in both intentional and unintentional overdose situations, warranting testing for the presence of these compounds (2–4). Imipramine, amitriptyline, doxepin, and clomipramine are metabolized via *N*-dealkylation to the active compounds desipramine, nortriptyline, desmethyldoxepin, and desmethylclomipramine, respectively. Desipramine and nortriptyline are sometimes also used as primary drugs. All these compounds undergo further metabolism either via dealkylation, ring (both aromatic and aliphatic) hydroxylation, and/or subsequent glucuronidation. The concentrations of both the parent compound and any active metabolite(s) must be considered when assessing serum TCA levels in patients (3).

Although quantitative serum assays (such as HPLC) are the most accurate at providing the specific TCA and the concentrations of the parent and metabolites, these assays are technically demanding, have longer turnaround times and are not available in most institutions (3). In cases of suspected overdose, laboratories without sophisticated toxicology instrumentation must offer alternative rapid testing. Several urine immunoassays that can report the presence or absence of TCA in less than 30 min are available, but the relationship between quantitative serum and qualitative urine levels of TCA-related compounds

and their metabolites has not been comprehensively studied.

Qualitative immunoassays are rapid, simple, and available on automated platforms or at the POC. However, these assays have some drawbacks. As opposed to HPLC, which identifies the individual TCA and its concentration, immunoassays are usually designed to identify many TCA, and as a result have a different detection sensitivity for each TCA and their metabolite(s). A positive result by immunoassay may represent one or more TCA at varying concentrations depending on the calibrator cutoff. An immunoassay that is very sensitive for detection of a certain TCA/metabolite might yield a positive urine result once the patient's serum reaches subtherapeutic or therapeutic levels. However, if the immunoassay is much less sensitive for a different TCA, an ingestion of that different TCA may not generate a positive result until the patient's serum reaches much higher levels than the TCA for which the assay is very sensitive at detecting. These intricacies can be problematic for clinicians who are only concerned about detecting patients with levels consistent with an overdose. The potential for false-positive results due to drugs such as cyclobenzaprine also exists.

Interpretation of urine TCA immunoassay results, especially in comparison to serum analysis, can be difficult. To our knowledge, no study has compared quantitative serum results with the qualitative urine results on different POC immunoassay devices. We found that for most TCAs, including doxepin, imipramine/desipramine, and nortriptyline, a subtherapeutic or therapeutic serum concentration will trigger a positive urine result at the manufacturers' cutpoints. Also in this study, 96% of patients (27 of 28) with a wide range of serum concentrations of amitriptyline/nortriptyline only (ranging from subtherapeutic to very toxic) had a positive urine result on both assays. In the one discrepant case, urine amitriptyline and nortriptyline levels were below detection limits according to both manufacturers' package inserts, so an unmeasured metabolite(s) must be responsible for the positive result. For virtually all positive urine TCA findings, it is not possible to determine whether the positive results correspond to subtherapeutic, therapeutic, supratherapeutic, or toxic serum concentrations using these qualitative immunoassays.

By contrast, therapeutic serum concentrations of clomipramine were typically associated with negative urine results. The Biosite device did not produce a positive urine result in any patient on clomipramine. Consistent with the package insert claims, the Syva device was slightly more sensitive to clomipramine and produced a positive result in 50% of patients (2 of 4). The quantitative urine concentrations correlated with the Syva results in that those with higher urine concentrations triggered a positive result. However, the cross-reactivity data in the package insert suggest that these concentrations of clomipramine and norclomipramine are not high enough to produce a positive result by themselves. Urinary clomipramine and norclomipramine concentrations are typically less than 1% of the original dose, suggesting that the 8-hydroxylated and glucuronidated metabolites, which are not detected by HPLC, represent most of the dose in urine (13). We speculate that these (unmeasured) metabolites account for the positive immunoassay. Patients on clomipramine, even those with serum concentrations that could produce toxicity, may be missed using either of these two urine immunoassays.

The specificity of the two POC devices that were tested was greater for the muscle relaxant, cyclobenzaprine, than for the TCA, clomipramine. Our results illustrated that the Biosite device produces more false-positive urine results secondary to cyclobenzaprine use than the Syva device. However, both assays were positive in the case with the highest concentration of cyclobenzaprine and the case with highly concentrated urine, which suggests that positive results may not be produced on either device until supratherapeutic serum concentrations are reached or patients develop extremely concentrated urines. Patients taking a combination of cyclobenzaprine and a TCA also trigger a positive result. In these cases, it is likely that either drug alone would have been sufficient to trigger a positive urine result.

The performance characteristics of each urine POC immunoassay device were compared to determine the sensitivity, specificity, and positive predictive value. Because our samples were chosen from patients with known positive serum results for TCA or cyclobenzaprine, interpretation of the negative predictive value is less meaningful. The Syva assay had a slightly higher sensitivity and positive predictive value, but the overall characteristics were similar for both assays. The difference in specificities can be explained by the higher rate of false positives secondary to cyclobenzaprine for the Biosite assay.

In most hospitals, the emergency department orders the majority of serum and/or urine toxicology screens, primarily to assess for drug toxicity. For this reason, the relationship between qualitative results and the likelihood of toxicity is important. We found that positive urine TCA findings can correlate with serum concentrations ranging from subtherapeutic to toxic. Consequently, if emergency room clinicians assume a positive result can be equated with toxicity, they may incorrectly suspect a TCA overdose or attribute clinical symptoms to TCA overdose, when in fact the patient is on a stable therapeutic dose and free of side effects. Furthermore, false-positive results due to the muscle relaxant cyclobenzaprine could be interpreted as a TCA overdose. Just as importantly, clinicians may assume the symptoms in a patient with high levels of clomipramine are not due to toxicity because the urine results are negative. Our results suggest that both positive and negative urine results from either the Biosite or Syva should be interpreted with caution by clinicians in the emergency department.

Conclusions

Because the specificity for each TCA is different using immunoassays, it is unlikely that a single cutpoint consistent with toxicity can be established. However, despite their disadvantages, most laboratories will still have to utilize urine and/or serum immunoassays to screen for TCA overdose. This study elucidated the correlation between quantitative serum results and qualitative urine results in order to help laboratorians and clinicians interpret the results provided by two different

POC urine immunoassay devices. In most cases, urine immunoassays should not be used alone to diagnosis TCA toxicity, but should be used in conjunction with clinical findings and/or quantitation of TCA serum levels.

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