

Comparison of Immunoassays for Semiquantitative Measurement of Benzoyllecgonine in Urine

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INTRODUCTION

One way of monitoring the effectiveness of a treatment for cocaine addiction is to analyze a patient's urine at regular intervals for benzoyllecgonine (BE), the major metabolite of cocaine. Total absence of BE from the urine indicates that the patient has stopped using cocaine, while a significant reduction in the urinary concentration of BE indicates that the patient is using less cocaine, and therefore is receiving some benefit from the treatment. To determine if there has been a reduction in the amount of cocaine used, it is necessary to employ a quantitative, or at least semiquantitative, method of analysis. However, because many factors can affect the concentration of a drug or any of its metabolites in urine, determination of urine concentrations can only provide an approximate indication of the amount of drug recently introduced into the body.

Analysis of urine for drugs of abuse most often involves an initial screening by an immunoassay to determine the presence or absence of the drug or its metabolites. If the drug is shown to be present by the immunoassay, a quantitative assay is often performed by gas chromatography/mass spectrometry (GC/MS). However, the cost of the GC/MS confirmation assay is high relative to the cost of an immunoassay screening test, and may be prohibitive where multiple specimens from each patient are to be analyzed.

The purpose of this study was to determine the feasibility of using a relatively inexpensive immunoassay to quantitatively determine the concentration of BE in urine from patients undergoing treatment for cocaine addiction.

Three different types of immunoassays were evaluated: (1) an enzyme immunoassay (EIA), (2) a fluorescence polarization immunoassay (FPIA), and (3) a kinetic interaction of microparticles

in solution immunoassay (KIMS). The antibodies used for each of the immunoassays were raised against BE, the major metabolite of cocaine. However, the study included determination of the cross-reactivity of each of the immunoassays to cocaine, ecgonine methyl ester, and ecgonine; each of these compounds can be present in the urine of a cocaine user in significant concentrations, a fact substantiated by quantitative GC/MS measurement of cocaine, norcocaine, BE, ecgonine methyl ester, and ecgonine in 39 urine samples previously shown to be positive for cocaine metabolites.

It was also important to determine the range of BE concentrations that could be measured by each of the immunoassays without performing a dilution, to indicate the number of dilutions that would be required to cover the range of BE concentrations anticipated in the urine from cocaine users.

Finally, the BE concentrations determined by GC/MS in urine samples from cocaine users were compared to the BE concentrations determined by each of the three immunoassays.

EXPERIMENTAL SECTION

Immunoassays

The EIA and KIMS analyses were performed at Northwest Toxicology, Inc., on a Hitachi 717 autoanalyzer. The EIA employed the Syva EMIT II cocaine reagents, while the KIMS used the Roche Diagnostics ONLINE cocaine reagents. Both immunoassays were performed according to manufacturers' recommended procedures except that 6-point calibration curves were used (0, 150, 300, 600, 1,000, and 2,000 ng/mL of BE). The FPIA analyses were performed at the Center for Human Toxicology, University of Utah, on an Abbott TDx analyzer using the Abbott TDx cocaine reagents and recommended procedure. For the immunoassay linearity study and the comparison of BE concentrations as determined by each of the immunoassays, samples were analyzed undiluted, after either 1:7 or 1:10 dilutions, and after 1:100 dilutions.

Gas Chromatography/Mass Spectrometry (GC/MS)

Urine concentrations of cocaine, norcocaine, BE, ecgonine methyl ester, and ecgonine were determined by GC/MS analysis performed at Northwest Toxicology using an extraction procedure similar to that reported in two recent publications (Okeke et al. 1994; Peterson et al. 1995). Deuterium-labeled isotopomers for each of the analytes were added to the urine samples as internal standards. The concentrations of the deuterated internal standards were: BE- $^2\text{H}_3$ and cocaine- $^2\text{H}_3$, each 100 ng/mL; norcocaine- $^2\text{H}_3$, ecgonine methyl ester- $^2\text{H}_3$, and ecgonine- $^2\text{H}_3$, each 50 ng/mL. The pH of the urine was made acidic by addition of 0.1 M acetate buffer (pH 4.0) and the cocaine and metabolites were extracted on Bond Elute LRC-SCX cation exchange solid-phase columns. The extraction columns were conditioned by washing with 2 mL of methanol followed by 2 mL of 0.1 M acetate buffer. After 1 mL of urine sample was added to each column, the columns were washed with 2 mL of 0.1 M HCl and 4 mL of methanol. The cocaine and metabolites were then eluted with 3 mL of methanol:ammonium hydroxide (98:2) freshly prepared just before using. The metabolites in each extract were derivatized by heating at 70 °C with 100 μL of hexafluoroisopropyl alcohol and 100 μL of pentafluoropropionic anhydride for 30 minutes. The derivatized extracts were then analyzed by GC/MS using a 5 percent phenyl methylsilicone fused silica capillary column (J&W Scientific, DB5MS, 12.5m x 0.2mm ID with a 0.33 μm film thickness) temperature programmed from 135 to 250 °C at 15 °C/min. The analytes were detected by electron ionization with selected ion monitoring performed on a Finnigan SSQ7000 GC/MS system. The ions monitored for each analyte and internal standard and the retention-time windows during which each set of ions was monitored are listed in table 1.

The concentrations of the analytes were determined from the ratio of the peak area of each analyte to the peak area of its corresponding deuterated internal standard; these ratios were compared with 6-point calibration curves that were generated from the analysis of urine fortified with known concentrations of the analytes and the internal standards.

The lower limit of quantitation for each analyte was 5 ng/mL.

TABLE 1. *GC/MS data for cocaine, derivatized metabolites, and their internal standards.*

Analytes and Internal Standards	Retention Time Windows	M/Z of Ions Monitored
Derivatized ecgonine	1.0 - 2.15 min.	318
Derivatized ecgonine- ² H ₃	1.0 - 2.15 min.	321
Derivatized EME	2.15 - 3.2 min.	345
Derivatized EME- ² H ₃	2.15 - 3.2 min.	348
Derivatized BE	5.7 - 6.9 min.	439
Derivatized BE- ² H ₃	5.7 - 6.9 min.	442
Derivatized norcocaine	6.9 - 9.0 min.	105
Derivatized norcocaine- ² H ₅	6.9 - 9.0 min.	110
Cocaine	6.9 - 9.0 min.	303
Cocaine- ² H ₃	6.9 - 9.0 min.	306

RESULTS AND DISCUSSION

Benzoyllecgonine Concentrations Quantifiable by the Immunoassays

Each of the immunoassays in this study is intended to be used to determine the presence of BE above or below a “cutoff” concentration of 300 ng/mL. To determine the range of linearity of each of the immunoassays, drug-free urine was fortified with known concentrations of BE ranging from 100 ng/mL to 200,000 ng/mL. Each fortified urine sample was analyzed in triplicate by each of the immunoassays using a 5-point calibration curve. Aliquots of each urine sample were also analyzed in triplicate by the EIA and KIMS immunoassays after either 1:10 or 1:100 dilution with drug-free urine. Only undiluted urine aliquots were analyzed by the FPIA. Table 2 compares the BE concentrations determined by each of the immunoassays with the concentrations determined by GC/MS and with the target (weighed-in) concentrations. The concentrations determined by EIA and KIMS in undiluted aliquots were in reasonable

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BE Target Conc.	GC/MS	EIA			Undi
		Undil.	1:10 dil.	1:100 dil.	
100	116	131			
200	235	282			
500	519	620			
1,000	1,075	1,143	1,117		1,0
2,000	2,147		2,363		
5,000	5,175		6,113	5,700	
10,000	10,096		10,927	12,400	
20,000	20,419			30,433	
50,000	50,454			71,867	
100,000	107,870			125,000	
200,000	266,885			277,400	

ntrations from 100 to 1,000 ng/mL, while the acceptable

concentrations determined by FPIA for undiluted aliquots extended to 2,000 ng/mL. By appropriate dilution, the range of acceptable agreement between GC/MS-determined concentrations and the EIA- and KIMS-determined concentrations extend to 100,000 ng/mL. It is reasonable to assume that analysis of diluted aliquots by FPIA would give comparable results.

Cross-Reactivities of the Immunoassays

To determine the cross-reactivities of each of the immunoassays, drug-free urine was fortified with either cocaine, ecgonine methyl ester, or ecgonine at concentrations ranging from 100 ng/mL to 1 mg/mL. Each fortified urine sample was analyzed in triplicate by each of the immuno-assays. Immunoassay responses equivalent to less than 50 ng/mL were considered below the limit of quantitation of the immunoassay and were reported as not detected (ND). The average percent cross-reactivities, calculated by dividing the indicated BE-equivalent concentration by the actual concentration of cocaine or the cocaine metabolite, are listed in table 3.

The percent cross-reactivities for the three immunoassays are similar and are all quite low, particularly at the higher analyte concentrations. Therefore, the measurement of BE in urine should not be significantly affected by cross-reactivity to the concentrations of cocaine, ecgonine methyl ester, and ecgonine, which are likely to be present in urine from cocaine users. The cross-reactivities of the immunoassays to norcocaine were not determined because the concentrations of this metabolite in urine are negligible.

Concentrations of Cocaine and Its Metabolites in Urine From Cocaine Users

The metabolism of cocaine in man has been extensively studied (Ambre et al. 1988; Jatlow 1988; Jindal and Lutz 1986; Jones 1984; Zhang and Foltz 1990). Ambre reported that after intravenous infusion of cocaine to five subjects, an average of 16 percent of the dose was excreted in the urine as BE, 15 percent as ecgonine methyl ester, and 2 percent as unchanged cocaine. In that study, as in most published investigations of the metabolism of cocaine, ecgonine concentrations were not determined due to analytical difficulties in measuring this very hydrophilic metabolite. In order to gain further insight into the relative concentrations of cocaine

TABLE 3. *Cross-reactivities of immunoassays.*

Spiked Conc. (ng/mL)	Percent Cross-Reactivities		
	Cocaine	Ecgonine	EME
KIMS BE Assay:			
100	ND	ND	ND
200	ND	ND	ND
500	ND	ND	ND
1,000	ND	5.7%	ND
2,000	3.1%	4.4%	
5,000	2.1%	2.7%	ND
10,000	1.8%	1.8%	ND
20,000	1.5%	1.4%	ND
50,000	1.1%	1.0%	0.2%
100,000	1.0%	0.9%	0.1%
200,000	1.0%	1.3%	0.1%
500,000	1.1%		0.0%
1,000,000			0.0%
Ave. % Cross- Reactivity =	1.6%	2.4%	0.1%
EIA BE Assay:			
100	ND	ND	ND
200	ND	ND	ND
500	ND	ND	ND
1,000	ND	ND	ND
2,000	ND	ND	ND
5,000	1.3%	ND	ND
10,000	1.6%	0.6%	ND
20,000	1.7%	0.7%	ND
50,000	1.3%	0.9%	ND
100,000	1.4%	0.7%	ND
200,000	1.2%	0.9%	ND
500,000	1.5%	0.8%	ND
1,000,000	1.4%	0.7%	0.0%
Ave. % Cross- Reactivity =	1.4%	0.8%	0.0%

TABLE 3. *Cross-reactivities of immunoassays (continued).*

Spiked Conc. (ng/mL)	Percent Cross-Reactivities		
	Cocaine	Ecgonine	EME
FPIA BE Assay:			
100	ND	ND	ND
200	ND	ND	ND
500	ND	ND	ND
1,000	ND	ND	ND
2,000	ND	ND	ND
5,000	ND	ND	ND
10,000	ND	ND	ND
20,000	ND	ND	ND
50,000	1.6%	1.5%	ND
100,000	1.6%	1.5%	ND
200,000	1.6%	1.5%	ND
500,000			ND
1,000,000			ND
Ave. % Cross- Reactivity =	1.6%	1.5%	0.0%

and its metabolites in urine from cocaine users, a newly developed GC/MS assay for cocaine, norcocaine, BE, ecgonine methyl ester, and ecgonine was used to analyze urine samples that had been previously found to be positive for cocaine metabolites. Table 4 lists the measured concentrations of cocaine and three of its metabolites in 39 urine samples. Norcocaine was also measured, but its concentrations are not listed in the table because most of them were below the limit of quantitation. The average concentrations of each compound expressed as a percent of the concentration of BE were: cocaine, 3.0 percent; norcocaine, 0.2 percent; ecgonine methyl ester, 19.1 percent; and ecgonine, 46.8 percent. However, the concentrations relative to the concentration of BE varied widely (cocaine, 0 to 16 percent; norcocaine, 0 to 2 percent; ecgonine methyl ester, 0 to 83 percent; and ecgonine, 0 to 215 percent).

Comparison of Benzoylecgonine Concentrations in Donor Samples Determined by GC/MS and Each of the Immunoassays

Table 5 compares the concentrations of BE in the 39 donor urine samples as determined by GC/MS and by each of the immunoassays.

TABLE 4. GC/MS measured concentrations of BE, cocaine, ecgonine methyl ester, and ecgonine in urine from cocaine users.

BE (g/mL)	Cocaine		EME		Ecgonine	
	(g/mL)	% of BE	(g/mL)	% of BE	(g/mL)	% of BE
0.27	0.05	16.9%	0.17	60.7%	0.13	48.9%
0.29	0.04	12.1%	0.24	82.7%	0.20	70.2%
0.30	0.02	6.7%	0.21	69.3%	0.26	85.3%
0.32	0.02	5.7%	0.09	27.3%	0.17	52.7%
0.34	<LOQ	0.0%	<LOQ	0.0%	<LOQ	0.0%
0.36	<LOQ	0.0%	0.06	17.8%	0.77	215.0%
0.36	<LOQ	0.0%	<LOQ	0.0%	<LOQ	0.0%
0.38	<LOQ	0.0%	<LOQ	0.0%	0.01	2.9%
0.41	0.01	3.2%	<LOQ	0.0%	0.01	2.5%
0.41	<LOQ	0.0%	0.01	2.9%	0.34	84.0%
0.45	0.01	2.4%	0.07	16.1%	0.30	66.7%
0.46	<LOQ	0.0%	<LOQ	0.0%	<LOQ	0.0%
0.55	<LOQ	0.0%	0.11	19.0%	0.29	52.9%
0.69	0.01	2.0%	0.09	12.9%	0.35	50.5%
0.77	<LOQ	0.0%	0.05	7.0%	0.13	16.9%
0.78	0.07	8.7%	0.36	46.0%	0.95	121.8%
1.02	0.10	9.8%	0.20	19.6%	1.44	141.2%
1.12	0.02	1.8%	0.12	10.7%	1.05	93.8%
1.14	0.02	1.8%	0.35	30.7%	0.20	17.5%
1.22	0.02	1.9%	<LOQ	0.0%	0.04	3.0%
1.28	0.02	1.5%	0.15	12.0%	0.28	21.5%
1.47	0.04	2.7%	0.03	2.0%	0.74	50.3%
1.54	0.03	2.1%	0.12	7.6%	1.07	69.5%
1.54	0.04	2.6%	0.34	22.1%	0.55	35.7%
2.55	0.12	4.7%	1.09	42.7%	0.98	38.4%
2.73	0.24	8.8%	0.23	8.4%	1.32	48.4%
2.73	0.03	1.1%	0.14	5.1%	0.96	35.2%
4.09	ND	0.0%	1.10	26.9%	0.52	12.7%
4.95	ND	0.0%	0.20	4.0%	1.02	20.6%
5.29	0.10	1.9%	0.26	4.9%	2.58	48.8%
6.40	ND	0.0%	0.05	0.8%	2.39	37.3%
6.60	0.16	2.4%	0.98	14.8%	3.15	47.7%

TABLE 4. GC/MS measured concentrations of BE, cocaine, ecgonine methyl ester, and ecgonine in urine from cocaine users (continued).

BE	Cocaine		EME		Ecgonine	
(g/mL)	(g/mL)	% of BE	(g/mL)	% of BE	(g/mL)	% of BE
8.44	0.09	1.1%	1.77	21.0%	5.23	62.0%
9.19	0.09	1.0%	0.89	9.7%	2.03	22.1%
10.13	0.10	1.0%	1.08	10.7%	3.11	30.7%
11.74	0.09	0.8%	1.97	16.8%	3.17	27.0%
14.37	0.11	0.8%	2.83	19.7%	2.61	18.2%
22.01	0.04	0.2%	3.12	14.2%	3.49	15.9%
93.81	9.67	10.3%	72.55	77.3%	55.09	58.7%
Average % of BE =		3.0%	19.1%		46.8%	
Range of % of BE =		0 to 16%	0 to 83%		0 to 215%	

The concentrations shown for the immunoassay determinations are the values obtained from analysis of an undiluted aliquot, or a 1:10 or 1:100 diluted aliquot. The immunoassay-determined concentrations from undiluted urine aliquots were used for samples found by GC/MS analysis to have BE concentrations between 0.1 and 1.0 g/mL. For samples found by GC/MS to have BE concentrations from 1.0 to 10.0 g/mL, the immunoassay-determined concentrations from 1:10 diluted aliquots were used, and for samples found by GC/MS to have BE concentrations from 10.0 to 100.0 g/mL, the immunoassay-determined concentrations from 1:100 diluted aliquots were used. No donor samples were available having BE concentrations above 100 g/mL. The percent differences between the concentrations determined by GC/MS and each immunoassay are also listed in table 5. The average of the percent differences for each immunoassay and the GC/MS measured concentration was FPIA,

-13 percent; EIA, 27 percent; and KIMS, 12 percent. The concentrations of BE determined by GC/MS were plotted against the concentrations determined by the KIMS assay in figure 1. The slope of the linear regression line is 1.003 and the r^2 is 0.979. The corresponding plot for EIA versus GC/MS is shown in figure 2; the slope is 1.414 and the r^2 is 0.978, and the plot for FPIA versus GC/MS (figure 3) gives a slope of 0.749 and an r^2 of 0.907. The data for the sample containing 93.8 ng/mL

TABLE 5. Measured concentrations (g/mL) of BE in donor samples.

BE Conc. by GC/MS	FPIA		EIA		KIMS	
	Conc.	% Dif.	Conc.	% Dif.	Conc.	% Dif.
0.27	0.30	0.10	0.37	0.36	0.38	0.40
0.29	0.27	-0.07	0.38	0.31	0.40	0.38
0.30	0.30	0.00	0.43	0.43	0.50	0.67
0.32	0.44	0.40	0.48	0.52	0.50	0.59
0.34	0.41	0.21	0.42	0.24	0.41	0.21
0.36	0.30	-0.16	0.40	0.11	0.45	0.25
0.36	0.31	-0.14	0.37	0.03	0.34	-0.06
0.38	0.11	-0.71	0.33	-0.13	0.31	-0.18
0.41	0.25	-0.38	0.39	-0.04	0.33	-0.19
0.41	0.51	0.25	0.69	0.70	0.64	0.57
0.45	0.66	0.45	0.60	0.32	0.65	0.43
0.46	0.31	-0.33	0.38	-0.18	0.37	-0.20
0.55	0.65	0.17	0.92	0.66	0.81	0.46
0.69	0.50	-0.27	0.75	0.09	0.74	0.07
0.77	0.22	-0.71	0.82	0.07	0.57	-0.26
0.78	0.77	-0.01	0.80	0.03	0.85	0.09
1.02	0.90	-0.12	0.96	-0.06	1.15	0.13
1.12	1.00	-0.11	1.65	0.47	1.44	0.29
1.14	1.80	0.58	1.79	0.57	2.09	0.83
1.22	0.60	-0.51	1.01	-0.17	1.07	-0.12
1.28	0.30	-0.77	0.70	-0.45	0.58	-0.55
1.47	0.70	-0.52	1.91	0.30	1.94	0.32
1.54	0.50	-0.67	1.61	0.05	1.51	-0.02
1.54	1.40	-0.09	2.40	0.56	2.04	0.32
2.55	2.50	-0.02	2.85	0.12	2.32	-0.09
2.73	2.00	-0.27	3.36	0.23	2.55	-0.07
2.73	3.00	0.10	3.60	0.32	2.38	-0.13
4.09	2.20	-0.46	5.45	0.33	4.50	0.10
4.95	5.00	0.01	7.55	0.53	6.19	0.25
5.29	3.50	-0.34	6.30	0.19	5.90	0.12
6.40	4.50	-0.30	8.11	0.27	5.31	-0.17
6.60	5.30	-0.20	9.23	0.40	7.43	0.13
8.44	4.80	-0.43	13.23	0.57	6.30	-0.25

TABLE 5. Measured concentrations (g/mL) of BE in donor samples (continued).

BE Conc.	FPIA		EIA		KIMS	
by GC/MS	Conc.	% Dif.	Conc.	% Dif.	Conc.	% Dif.
9.19	11.60	0.26	11.31	0.23	10.00	0.09
10.13	8.00	-0.21	10.10	0.00	9.00	-0.11
11.74	8.00	-0.32	18.20	0.55	13.70	0.17
14.37	7.00	-0.51	17.90	0.25	13.30	-0.07
22.01	18.00	-0.18	33.20	0.51	22.80	0.04
93.81	195.00	1.08	210.70	1.25	134.60	0.43
Average % Difference with						
GC/MS determined conc. -				27%		12%
13%						

of BE (table 5) are not included in the linear regression plots because they strongly biased the correlation determination.

Limitations to the Interpretation of the Urine Drug and Metabolite Concentrations

In addition to the size of dose and the elapsed time between use of cocaine and collection of the urine, many other factors can affect the concentration of cocaine and its metabolites in urine specimens. They include route of administration, intersubject differences in metabolism, volume of fluid intake prior to giving a urine specimen, and chemical hydrolysis occurring in the urine prior to analysis.

The urine samples were received at Northwest Toxicology as part of its workplace drug-testing business. From the time a urine specimen is collected to the time the testing is completed is typically 3 to 4 days. During this time the specimens are not refrigerated. The donor urine specimens used in this study were stored frozen after they were initially found to be positive for cocaine metabolites. After collecting positive samples over a 4-week period, the immunoassays and GC/MS analyses described here were performed over an additional 4-week period, during which the urine samples were stored at normal refrigerator temperatures. The measured concentrations of BE in these samples decreased by an average of only 2 percent and a maximum of 13 percent from the time the initial GC/MS confirmation was performed until the time the GC/MS determination of cocaine and its four metabolites was performed.

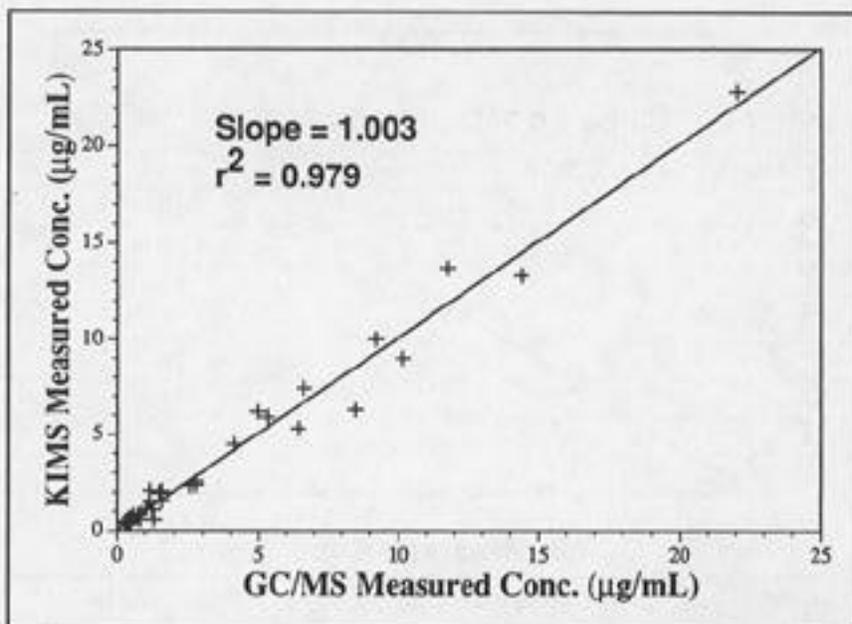


FIGURE 1. BE concentrations determined by KIMS versus GC/MS.

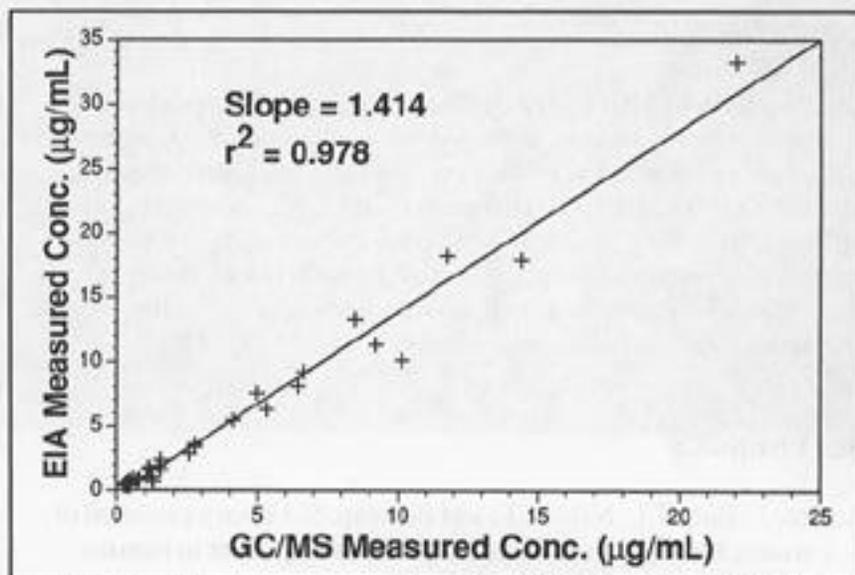


FIGURE 2. BE concentrations determined by EIA versus GC/MS.

CONCLUSIONS

The data presented here show that three commercially available immunoassays can be used with appropriate dilutions to obtain semi-quantitative measurement of BE in urine over a concentration range of at least 0.1 to 1000 &g/mL. Even though cocaine, ecgonine methyl ester, and ecgonine can be present in urine from cocaine users at widely varying concentrations, they have only a minor effect on the immunoassay responses due to their low cross-reactivity to the antibodies used in these immunoassays.

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ACKNOWLEDGMENT

The research described here was supported in part by National Institute on Drug Abuse contract no. N01-DA-1-9205.

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