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Fingerstick Plasma Drug Testing of Chronic Pain Patients: Comparison of Paired Fingerstick Plasma and Urine Specimens

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ABSTRACT

Aim
A clinical study was conducted to evaluate fingerstick blood as a viable biological matrix for monitoring prescription and illicit drugs in a clinical setting on patients undergoing pain and addiction treatment. The current standard for monitoring patients' medication use, misuse, and diversion is urine drug testing (UDT).

Materials and Methods
This study compared 632 paired urine and fingerstick blood specimens collected at three pain management clinics and one suboxone clinic for 35 drugs and/or metabolites. Plasma from the fingerstick blood was used for the analysis. The urine and plasma specimens were analyzed by validated liquid chromatography–tandem mass spectrometry (LC-MS-MS) procedures. The urine cutoff used by most pain testing laboratories were used to identify positive and negative drugs in urine. Limit of quantitation was used to identify positive and negative drugs in plasma. Drugs and/or metabolites were quantified in both urine and plasma using deuterium-labeled internal standards.

Results
Results were tabulated for urine and plasma specimens for data analysis. The results showed that 8.7% of plasma specimens detected more drugs compared to the corresponding urine specimens, and 2.2% of the urine specimens detected a drug that was negative in the corresponding plasma specimen. Overall 89.1% of the specimens had complete agreement between urine and plasma specimens for detection. The observed Cohen's Kappa value for overall drug detection was 0.96 an "almost perfect" agreement as characterized by Landis and Koch.

Conclusion
Based on the observed data, the authors conclude that plasma collected from fingerstick blood is a better matrix to monitor patients currently prescribed pain medications or patients currently undergoing medication-assisted opioid treatment compared to urine drug testing.

Keywords
Fingerstick blood; Pain management; Prescription drugs; Opioids; Opiates; Illicit drugs.

INTRODUCTION

Opiates, opioids, and other pain medications are widely prescribed for acute and chronic pain. Physicians try to minimize the risk of misuse, diversion, and addition. While clinical observations and patient's self-report are valuable clinical tools, toxicology tests provide objective diagnostic data for the recent use of prescribed and illicit drugs.[1] Urine drug testing is predominantly used to access the use and misuse of the prescribed drugs and the use of illicit drugs.[2] Oral fluid has been proven to be another biological metric in pain management drug monitoring.[3,4] Blood specimens are used by medical examiners to determine the cause of drug-re-

lated overdose death and the concentration of drug(s) and its metabolites provide the relevant information on therapeutic and toxic levels.[5] Serum and plasma have been used for the last fifty years to monitor the therapeutic level for anticonvulsants, antidepressants, cardiac and other prescription drugs. The committee on the "Laboratory Medicine Practice Guideline" for pain management drug monitoring recommended urine as the gold standard for prescription and illicit drug monitoring. However, the same journal[6] called for further research in using serum or plasma to monitor pain management drugs since pharmacokinetic (PK) studies on the opiates, opioids, and benzodiazepines are documented with serum or plasma.

Blood collection from the vein is an invasive collection protocol, requiring many pain clinics to staff a phlebotomist. Fingerstick blood has been used for monitoring drug levels.[7] Fingerstick blood collection is minimally invasive, and it is an observed collection. As a result, fingerstick blood collection eliminates the specimen adulteration concern with urine specimens.

This study compared plasma from fingerstick blood tests to the urine drug tests on patients undergoing chronic pain treatment and patients utilizing medication-assisted opioid treatment. The specimens were analyzed for 35 drugs and/or metabolites by highly sensitive liquid chromatography-tandem mass spectrometry (LC-MS-MS) procedures.

MATERIALS AND METHODS

Patient and Specimen Collection

The study collected 634 paired fingerstick blood and urine specimens from patients from three pain clinics in three different states (TX, OH, MA of USA), and one suboxone clinic (WV) during the period of March 2017 to November 2017. The patients signed an informed consent form and agreed to participate in the study. Institutional review board approval was obtained from Western IRB (WIRB20180276).

Two to three drops of fingerstick blood was collected in an FDA 510K cleared microtube with heparin as an anticoagulant. Subsequently, a urine specimen was collected within 30 min of the fingerstick blood collection. Both fingerstick blood and the urine specimens were shipped to Firstox laboratories (Irving, Texas, USA).

Laboratory Analysis

Fingerstick blood specimens were centrifuged to separate the plasma and 10 ul of plasma was used for the analysis. Deuterium labeled internal standards were added to the specimen. Drugs and metabolites were extracted using solid-phase extraction followed by protein precipitation using cold acetonitrile. The extract was placed in an evaporator for 20 to 30-minutes at 45 °C to remove the solvent. The residue was dissolved in the mobile phase and 20 ul of the extract was injected into the LC-MS-MS.

Table 1. *Expanded Agreement Chart*

Analyte	Serum and Urine Negative	Serum and Urine Positive	Serum Only Positive	Urine Only Positive	Observed Proportionate Agreement (p0)	Probability of Random Agreement (pe)	Cohen's Kappa (K)	Strength of Agreement
Oxycodone	462	159	10	1	0.98	0.61	0.95	"Almost Perfect"
Hydrocodone	570	56	5	1	0.99	0.83	0.94	"Almost Perfect"
Fentanyl	598	32	1	1	1.00	0.90	0.97	"Almost Perfect"
Tramadol	607	23	2	0	1.00	0.93	0.96	"Almost Perfect"
Methadone	624	8	0	0	1.00	0.98	1.00	"Almost Perfect"
Buprenorphine	261	371	0	0	1.00	0.52	1.00	"Almost Perfect"
Naloxone	277	338	9	8	0.97	0.50	0.95	"Almost Perfect"
Morphine	573	56	3	0	1.00	0.83	0.97	"Almost Perfect"
Hydromorphone	550	72	3	7	0.98	0.79	0.93	"Almost Perfect"
Codeine	624	6	1	1	1.00	0.98	0.86	"Almost Perfect"
Diazepam	575	54	3	0	1.00	0.84	0.97	"Almost Perfect"
Clonazepam	580	47	3	2	0.99	0.86	0.95	"Almost Perfect"
Alprazolam	590	40	1	1	1.00	0.88	0.97	"Almost Perfect"
Lorazepam	613	19	0	0	1.00	0.94	1.00	"Almost Perfect"
Amphetamine	529	83	17	3	0.97	0.75	0.87	"Almost Perfect"
Methamphetamine	582	42	8	0	0.99	0.86	0.91	"Almost Perfect"
Benzoylecgonine	604	14	14	0	0.98	0.94	0.66	"Substantial"
Gabapentin	330	295	2	5	0.99	0.50	0.98	"Almost Perfect"
Pregabalin	586	43	3	0	1.00	0.87	0.96	"Almost Perfect"
Carisoprodol	628	4	0	0	1.00	0.99	1.00	"Almost Perfect"
Tapentadol	628	4	0	0	1.00	0.99	1.00	"Almost Perfect"
Ketamine	628	4	0	0	1.00	0.99	1.00	"Almost Perfect"
Overall	11836	1771	88	33	0.99	0.77	0.96	"Almost Perfect"

Urine was diluted to 1 to 50 ul for analysis. Deuterated internal standards were used for qualification. Ten (10) ul of the extract was injected to the LC-MS-MS.

LC-MS-MS analyses were performed with Sciex 6500 Plus and two Agilent 1290 Infinity pumps. The mobile phase was 0.1% formic acid in water and 0.1% formic acid in methanol. The High-performance liquid chromatography (HPLC) column was Agilent phenyl-hexane 4.6×50 mm.

Data Analyses

Cohen's Kapa values were calculated for each drug and metabolites (Table 1). Cohen's Kappa value is interpreted according to Landis and Koch as follows: less than 0 as poor, 0.00 to 0.2 as slight, 0.21-0.40 as fair, 0.41-0.60 as moderate, 0.61-0.80 as substantial, and 0.81-1.00 as an almost perfect agreement. In addition, mean, standard error of the mean (SEM), median, and lowest concentrations and highest concentrations for each drug and metabolites were tabulated Table 2.[8-10]

Table 2. *Summary of Drug and Metabolite Concentrations in Plasma and Urine Specimens*

	Serum				Urine				
Analyte	**N**	**Mean±SEM (ng/mL)**	**Minimum (ng/mL)**	**Maximum (ng/mL)**	**N**	**Mean±SEM (ng/mL)**	**Median (ng/mL)**	**Minimum (ng/mL)**	**Maximum (ng/mL)**
Oxycodone	165	42.17±6.91	0.18	661.70	151	2092.73±188.09	1378.50	1.10	10373.50
Noroxycodone	164	31.79±2.79	0.22	268.70	158	4499.66±436.89	2180.40	12.10	29295.40
Oxymorphone	167	19.42±2.96	0.03	355.00	157	1357.47±154.92	619.20	1.20	12871.20
Hydrocodone	61	45.45±13.91	1.12	774.00	57	1214.46±166.54	706.05	1.30	4659.10
Norhydrocodone	61	9.28±1.46	0.40	77.70	56	1642.99±266.35	1046.60	11.60	9760.00
Fentanyl	33	17.57±9.19	0.10	255.70	33	48.55±13.41	24.90	1.60	353.80
Norfentanyl	31	1.28±0.48	0.02	13.70	34	296.16±90.85	131.00	2.00	2977.40
Tramadol	25	252.15±86.93	9.00	2160.00	23	8950.96±2335.73	5000.00	2.20	42819.60
O-Desmethyltramadol	25	165.99±78.66	0.53	1972.00	21	10012.65±2819.15	4226.90	33.40	46723.50
Methadone	8	96.73±26.19	6.00	242.40	8	1441.56±310.16	1054.90	181.00	2956.60
EDDP	8	18.11±5.93	2.10	46.60	8	3250.71±1347.12	1956.35	129.00	12692.20
Buprenorphine	369	14.69±3.25	0.10	971.00	369	317.56±27.06	166.05	2.10	6705.30
Norbuprenorphine	369	8.80±0.53	0.04	137.80	370	1014.23±407.08	383.00	3.00	146139.30
Naloxone	347	8.76±1.28	0.02	223.60	346	438.12±32.32	284.30	1.30	7373.90
Morphine	59	266.05±41.57	0.10	1953.10	56	13035.63±2249.51	8137.20	3.80	93875.80
Hydromorphone	80	16.91±4.81	0.03	342.10	79	1266.06±262.78	287.70	3.00	14630.50
Codeine	7	150.12±73.22	0.23	597.90	7	13341.09±6128.58	5317.00	88.20	43464.00
Diazepam	54	288.70±63.75	0.17	2547.90					
Nordiazepam	58	384.55±69.80	0.03	2587.60	53	775.59±185.24	172.10	1.70	5000.00
Oxazepam	56	55.28±12.77	0.20	444.70	57	1362.69±257.81	433.00	5.00	8971.40
Temazepam	53	92.73±20.23	0.10	740.00	51	1171.03±231.31	434.00	1.10	8395.00
Clonazepam	47	11.22±1.24	0.77	44.30					
7-Aminoclonazepam	50	15.96±1.75	1.09	60.80	49	374.43±62.72	271.90	32.70	2307.90
Alprazolam	39	26.54±5.09	0.58	149.30					
Alpha-Hydroxyalprazolam	32	3.06±0.63	0.10	19.00	41	350.83±72.42	179.80	1.60	2102.30
Lorazepam	19	47.63±11.40	1.90	177.20	19	748.12±244.64	490.70	17.20	4966.20
Amphetamine	100	80.60±17.96	0.71	1538.70	86	6013.54±951.91	2150.55	15.20	44126.20
Methamphetamine	50	352.09±138.43	2.40	6395.70	42	9996.97±3337.52	817.80	5.50	99112.10
Benzoylecgonine	28	73.85±21.79	2.40	563.20	14	21668.63±9862.92	8506.45	0.60	142434.80
Gabapentin	297	1357.14±78.76	1.29	13712.00	300	43418.92±3871.90	10152.00	9.20	533675.20
Pregabalin	46	2419.56±366.37	2.50	10790.00	43	68364.87±9744.12	57794.80	33.60	280906.20
Carisoprodol	4	1079.26±472.11	3.73	2140.20	3	591.93±223.62	775.60	53.20	947.00
Meprobamate	3	3215.00±258.18	2610.00	3677.00	3	27443.9±11443.46	14684.00	12209.60	55438.10
Tapentadol	4	374.98±120.36	114.90	668.50	4	17749.40±11041.31	5000.00	5000.00	55997.60
N-desmethyltapentadol	4	119.35±66.58	11.20	340.40	4	3985.23±1189.89	3639.30	1292.10	7370.20
Ketamine					4	152.40±74.29	108.95	8.70	383.00
Norketamine	4	15.93±4.09	2.50	24.30	4	95.45±14.05	83.20	72.00	143.40
Butalbital	12	921.98±222.48	61.10	2787.70	6	1061.15±413.15	683.50	239.40	3256.70

RESULTS

Agreement Between Plasma and Urine

Comparison of LC-MS/MS results for fingerstick plasma with those of the corresponding urine specimen is shown in Table 3. Cutoff values showing the limit of quantitation used for the Cohen's Kapa calculations are shown in Table 4. Benzoylecgonine, a cocaine metabolite, was observed more frequently in plasma *versus* urine at the established cutoff values. The cutoff for benzoylecgonine was 50 ng/ml in urine and 2 ng/ml in plasma. More frequent positive results were observed in plasma specimens for methamphetamine with the limit of quantitation (LOQ) of 50 ng/ml in urine and 2 ng/ml in plasma. Few specimen pairs had a positive result in urine specimen without any detection in the corresponding plasma specimen (Table 5). Examining these results, it was observed that six pairs were gabapentin positive with a very low urine concentration around 50 to 100 ng/ml, and eight pairs were naloxone positive at very low concentrations in urine. In seven specimens, hydromorphone was detected in urine as a metabolite of hydrocodone or morphine, and the corresponding plasma specimens did not detect any hydromorphone. Clinically, none of the hydromorphone positives in which hydromorphone was detected as a metabolite of morphine or hydrocodone were signification

Table 3. *Agreement Between Plasma and Urine Drug Detection by Individual Metabolite*

Analyte	Total Positives	Serum Only Positive		Urine Only Positive		Serum and Urine Positive	
Oxycodone	168	17	10.1%	3	1.8%	148	88.1%
Noroxycodone	167	9	5.4%	3	1.8%	155	92.8%
Oxymorphone	169	12	7.1%	2	1.2%	155	91.7%
Hydrocodone	62	5	8.1%	1	1.6%	56	90.3%
Norhydrocodone	61	5	8.2%	0	0.0%	56	91.8%
Fentanyl	34	1	2.9%	1	2.9%	32	94.1%
Norfentanyl	34	0	0.0%	3	8.8%	31	91.2%
Tramadol	25	2	8.0%	0	0.0%	23	92.0%
O-Desmethyltramadol	25	4	16.0%	0	0.0%	21	84.0%
Methadone	8	0	0.0%	0	0.0%	8	100.0%
EDDP	8	0	0.0%	0	0.0%	8	100.0%
Buprenorphine	370	1	0.3%	1	0.3%	368	99.5%
Norbuprenorphine	371	1	0.3%	2	0.5%	368	99.2%
Naloxone	355	9	2.5%	8	2.3%	338	95.2%
Morphine	59	3	5.1%	0	0.0%	56	94.9%
Hydromorphone	87	8	9.2%	7	8.0%	72	82.8%
Codeine	8	1	12.5%	1	12.5%	6	75.0%
Nordiazepam	58	5	8.6%	0	0.0%	53	91.4%
Oxazepam	58	1	1.7%	2	3.4%	55	94.8%
Temazepam	55	4	7.3%	2	3.6%	49	89.1%
Clonazepam^	52	3	5.8%	2	3.8%	47	90.4%
7-Aminoclonazepam							
Alprazolam^	42	1	2.4%	1	2.4%	40	95.2%
Alpha-Hydroxyalprazolam							
Lorazepam	19	0	0.0%	0	0.0%	19	100.0%
Amphetamine	103	17	16.5%	3	2.9%	83	80.6%
Methamphetamine	50	8	16.0%	0	0.0%	42	84.0%
Benzoylecgonine	28	14	50.0%	0	0.0%	14	50.0%
Gabapentin	302	2	0.7%	5	1.7%	295	97.7%
Pregabalin	46	3	6.5%	0	0.0%	43	93.5%
Carisoprodol	4	1	25.0%	0	0.0%	3	75.0%
Meprobamate	3	0	0.0%	0	0.0%	3	100.0%
Tapentadol	4	0	0.0%	0	0.0%	4	100.0%
N-desmethyltapentadol	4	0	0.0%	0	0.0%	4	100.0%
Norketamine	4	0	0.0%	0	0.0%	4	100.0%

^For Clonazepam and Alprazolam, the specimen was considered positive in plasma if either parent drug or metabolite was positive.

Table 4. *LOQ for Drugs/Metabolites in Plasma and Urine*

Drug/Metabolite	Serum LC-MS/MS LOQ (ng/mL)	Urine LC-MS/MS LOQ (ng/mL)	Drug/Metabolite	Serum LC-MS/MS LOQ (ng/mL)	Urine LC-MS/MS LOQ (ng/mL)
Oxycodone	2	50	Diazepam	2	N/A
Noroxycodone	2	50	Nordiazepam	2	50
Oxymorphone	2	50	Oxazepam	2	50
Hydrocodone	2	50	Temazepam	2	50
Norhydrocodone	2	50	Clonazepam	2	N/A
Fentanyl	0.1	2.5	7-Aminoclonazepam	2	50
Norfentanyl	0.2	2.5	Alprazolam	2	N/A
Tramadol	2	50	Alpha-Hydroxyalprazolam	2	50
O-Desmethyltramadol	2	50	Amphetamine	2	50
Methadone	2	50	Methamphetamine	2	50
EDDP	2	50	Benzoylecgonine	2	50
Buprenorphine	0.1	2.5	Gabapentin	50	100
Norbuprenorphine	0.2	2.5	Pregabalin	5	50
Naloxone	0.2	2.5	Carisoprodol	5	50
Morphine	2	50	Meprobamate	5	50
Hydromorphone	2	50	Tapentadol	2	50
Codeine	2	50	N-desmethyltapentadol	2	50
Lorazepam	2	50	Norketamine	2	50

for patient compliance with the drug. Overall, the agreement with a Cohen's Kappa value of 0.96 between fingerstick plasma specimens and the urine specimens is an excellent agreement.

Table 5. *Summary of Plasma and Urine Agreement*

Total Number of Specimen Pairs	632	
Specimen Pairs with Plasma/Urine Positive Agreement	553	89.1%
Specimen Pairs with Plasma Only Positives	55	8.7%
Specimen Pairs with Urine Only Positives	14	2.2%

**Note: Drug/Metabolite combinations were considered one drug. Individual metabolites were not counted as multiple positives. For example: Oxycodone, Oxymorphone, and Noroxycodone were considered one drug.*

DISCUSSION

Fingerstick plasma specimens were evaluated to be used as an alternative to urine for compliance monitoring of pain patients' prescription and illicit drug use. LC-MS/MS was used to analyze both fingerstick plasma and urine. Typically, pain testing toxicology labs screen urine by immunoassay and confirm by LC-MS/MS. This work compared both fingerstick plasma and urine specimens using the same high sensitivity LC-MS/MS methods. As a result, this protocol eliminated false-negative results in urine due to the high immunoassay cutoff and low cross-reactivity with some opiates, opioids, and benzodiazepines.[11]

Adulteration and substitution are great concerns with urine drug testing.[12] Fingerstick blood collection is directly observedand eliminates adulteration and substitution. Pharmacokinetic studies for all prescription drugs have been submitted for Food and Drug Administration (FDA) approval, and the drug concentrations are documented in serum or plasma. In addition, all the pain management drugs have established therapeutic and toxic levels in published literature. Furthermore, serum or plasma has established steady-state levels while there is no reliable relationship between urine drug concentration and dose of drug that was ingested or administered.[1] Therefore, the concentrations of drugs in plasma have much more pharmacological meaning than the drug concentrations in urine. Drugs like gabapentin and pregabalin are detected in very high concentrations for the prescription doses. Typical toxicology labs report the concentration as greater than 10000 ng/ml, which does not provide any information beyond a qualitative result. The fingerstick plasma result report provides therapeutic and toxic ranges for the prescribed drugs.[13]

It has been reported that many pain management physicians were charged and convicted if a pain patient died. Documentation of the blood concentrations reduces the physician's liability in case of adverse events with the patients.[14]

CONCLUSION

Fingerstick plasma drug testing provides a clinically effective way to monitor patients currently prescribed pain medications or undergoing medication-assisted opioid treatment for both prescription and illicit substances. Compared to UDT, fingerstick plasma drug testing produces nearly identical positive results, and can detect lower concentrations of drugs, providing physicians with a reliable means of medication monitoring and detection of illicit substances.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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