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A Comparison of Meconium, Maternal Urine and Neonatal Urine for Detection of Maternal Drug Use During Pregnancy

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ABSTRACT: A large scale drug screening study was done to determine the prevalence of drug use in a large metropolitan, obstetric population. Meconium and first voided urine, as well as maternal urine were collected from 423 consecutive deliveries. Urine samples and methanolic extracts of meconium were initially screened by Enzyme Multiplied Immunoassay Technique (EMIT) and then confirmed by Gas Chromatography/Mass Spectrometry (GC/MS). Analysis of cocaine metabolite as benzoylecogonine, cannabinoid as carboxy-THC, codeine, morphine and methadone were included in the study. The positive rate for benzoylecgonine was virtually identical for meconium, maternal urine and neonatal urine (12%). Analysis of meconium was found to be more reliable than analysis of maternal or neonatal urine for the detection of benzoylecgonine. Meconium did not appear to offer an advantage over maternal or neonatal urine for detection of cannabinoid, codeine, morphine, or methadone.

KEYWORDS: toxicology, meconium, urine, drug use, chromatographic analysis, drug screening

Physicians involved in the primary care of newborn infants face the difficult problem of identifying those born to drug-dependent mothers. Ostrea and others [*1–6*] have cited numerous prenatal complications associated with maternal drug abuse during pregnancy. These include fetal distress, high incidence of stillbirths, maternal hemorrhage, meconium staining of the amniotic fluid, and premature rupture of the membranes. In addition, numerous complications of the newborn such as low birth weight, high incidence of asphyxia, prematurity, congenital malformations and increased risk of immunodeficiency disease have been reported [*7–11*]. Therefore, it is imperative for proper intervention and follow-up that infants born to women who have used drugs during pregnancy should be identified as early as possible.

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A number of factors make this determination difficult. Mothers may be extremely reluctant to admit to the use of drugs or provide a urine sample for fear of punitive consequences. Obtaining a urine specimen from the neonate at the proper time is not always possible. In addition, analysis of the neonate's urine sample may produce a false negative, depending on the time of the last ingestion of the drug by the mother or the length of time after birth that the specimen was collected [*12*].

Recently several groups have investigated the analysis of drugs and metabolites in newborn meconium as a way of determining intrauterine exposure to drugs [*1,2,13–18*]. In these studies, meconium was clearly shown to be a suitable sample for the detection of drugs of abuse, such as, cocaine, codeine, morphine, and marijuana. Meconium offers the major advantage over urine of greater reliability of collection. In addition, the earliest reports of meconium testing used radioimmunoassay (RIA) fluorescence polarization immunoassay (FPIA) or enzyme immunoassay (EMIT) to screen for drugs of abuse. To date, Maynard et al. [*18*], Varley et al. [*19*], Steele et al. [*20*], and Callahan et al. [*21*] have confirmed the preliminary screening results by GC/MS. In order to compare their relative usefulness for detection of maternal drug used during pregnancy, our study consisted of maternal urine, meconium and first voided urine collected from 423 consecutive births at a metropolitan hospital. EMIT was used to screen urine specimens and methanolic extracts of meconium specimens for drugs of abuse. Samples which showed activity above negative were then confirmed by our standard GC/MS procedure for the parent drug or drug metabolite of interest.

Materials and Methods

Materials

All chemicals and solvents were of analytical or higher grade and were purchased from Fisher Scientific or Sigma Company. BSTFA was purchased from Supelco. Deuterated internal standards: Benzoylecgonine-d_3, Methadone-d_3, Codeine-d_3 and Morphine-d_3 were purchased from Radian Corporation. Carboxy-THC-d_3 was obtained from Research Triangle Institute.

Detectabuse Type R Extraction Columns were purchased from Biochemical Diagnostics. Bond Elut Certify LRC columns were obtained from Varian Corporation.

Specimen Collection and Storage

In order to assess the prevalence of maternal drug use, newborn meconium and first voided urine as well as maternal urine were collected from 423 consecutive deliveries at Bronx Lebanon Hospital Center. In April 1991 and May 1991 a total of 345 meconium specimens, 351 newborn urine specimens and 303 maternal urine specimens were collected and tested at Roche Biomedical Laboratories. Samples were stored short term for up to approximately two weeks at 2° to 8°C. Long term storage was frozen at <-20°C.

A detailed history of drug use during pregnancy was obtained from all mothers by maternal social workers and neonatologists at Bronx Lebanon Hospital Center. All specimens and information were numerically coded to insure anonymity. The laboratory results of these specimens were not used in clinical treatment.

Analysis of Meconium

0.5–1.0 g of meconium was weighed and vortexed rigorously in 5 mL of methanol. After centrifugation at low speed, the supernatant was dried under nitrogen at 40°C. The sample was then reconstituted with 1.0 mL of methanol. 0.5 mL was taken off for

screening and the remaining portion was saved for confirmation of presumptive positives by GC/MS.

Screening of the meconium extract was done on the Olympus AU5000 using a mixture of 0.5 mL of methanolic extract and 0.5 mL of EMIT buffer. The usual screening cutoffs were not applied. Instead, specimens demonstrating activity above the negative control were confirmed by GC/MS for the drug of interest. GC/MS confirmation of the drug was carried out by evaporating the methanolic extract to dryness at 40°C under a stream of nitrogen. The analysis was then carried out using the procedure described below.

Immunoassay Screening

Immunoassay screening of urine and meconium was done on the Olympus AU5000 using EMIT reagents purchased from Syva Company. Calibrators and controls were either purchased from Syva Company or made in-house. Screening data was obtained in milliabsorbance units which provided qualitative results. Specimens demonstrating activity at least ten milliabsorbance units above the negative control were then confirmed by GC/MS for the parent drug or metabolite of interest.

Confirmation by Gas Chromatography/Mass Spectrometry

Methanolic extracts of meconium (taken to dryness under nitrogen) and urines were confirmed using a Hewlett Packard Model 5890 Gas Chromatograph with a Model 5970 Mass Spectrometer. Either a HP-1 or a HP-5 capillary column was used.

Confirmation of benzoylecgonine was carried out on either a methanolic extract of meconium or 1.0 mL of urine specimen. Deuterated benzoylecgonine (500 ng/mL) and 0.4 mL of 0.1 M phosphate buffer (pH 6.0) were added to the sample. After mixing, the buffered sample was then added to a Bond Elut Certify solid phase extraction column which had been preconditioned sequentially with methanol and 0.1 M phosphate buffer (pH 6.0). The column was then washed sequentially with distilled water, 0.1 M HCl and methanol. Benzoylecgonine was then eluted with 2 ml methylene chloride-isopropyl alcohol (80:20) with 2% ammonium hydroxide. The eluent then taken to dryness at 40°C with a stream of nitrogen. The sample was suspended in 50 μL of BSTFA and heated at 70°C for 20 min to form a trimethylsilyl derivative of benzoylecgonine. The sample was allowed to cool, reconstituted with 200 μL of iso-octane and transferred to a GC vial with micro-insert. One or two μL of this solution was injected into the HP GC/MS operating in the SIM mode. Chromatography was performed with initial temperature at 80°C for one minute followed by 40°C/min ramp to 280°C. Ions monitored were: 243 and 364 for the deuterated internal standard 240, 346 and 361 for benzoylecgonine. Quantitation was done using 240:243 peak area ratio.

Confirmations of codeine and morphine were carried out on either a methanolic extract of meconium or 1.0 mL of urine. Deuterated codeine (1000 ng/mL) and deuterated morphine (1000 ng/mL), 3 mL of deionized water and 0.7 mL of concentrated HCl were added to the sample. After mixing, the samples were hydrolyzed in an autoclave at 120°C for 20 min. After cooling, the pH of the samples was adjusted to 9.0 by adding: 1.5 mL of 1.5 M Tris buffer (pH 9), 1.5 ml KOH saturated with K_2CO_3. The samples were then applied to Bond Elut Certify columns which had been preconditioned sequentially with methanol, deionized water and Tris buffer. The columns with absorbed samples were sequentially washed with deionized water, pH 4 acetate buffer and methanol. This wash process was repeated two more times. Codeine and morphine were then eluted with 2 mL of chloroform:isopropanol:diethylamine (90:10:2). The eluents were then taken to dryness at 60°C under a stream of nitrogen. The samples were then suspended in 50 μL of BSTFA and heated at 70°C for 20 min to form trimethylsilyl derivatives of codeine

and morphine. The samples were allowed to cool, reconstituted with 200 μL of iso-octane and transferred to GC vials with micro-inserts. One or two μL of this solution was injected into the HP GC/MS operating in the SIM mode. Chromatography was performed with initial temperature at 80° for one minute followed by a 40°C/min ramp to 290°C. Ions monitored for codeine were 346 and 374 for the deuterated internal standard and 343, 356 and 371 for codeine. Quantitation for codeine was done using 371:374 ratio. Ions monitored for morphine were 417 and 432 for the deuterated internal standard and 401, 414 and 429 for morphine. Quantitation for morphine was done using the 429:432 peak area ratio.

Confirmation of 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (Carboxy-THC) was carried out using either a methanolic extract of meconium or 10 mL of urine. Deuterated carboxy-THC (50 ng/mL) and 2 mL of 6 N NaOH were added to the sample followed by incubation at 60°C for 30 min. After cooling, 1.6 mL of glacial acetic acid was added to the sample. The sample was then applied to Type R Detectabuse Extraction Columns which had been preconditioned with acetate buffer (0.2 M, pH 4). The column containing the absorbed Carboxy-THC, was then washed with 50% methanol and allowed to dry thoroughly under vacuum. Carboxy-THC was eluted from the column with ethyl acetate:isopropanol (85:15) and the eluent taken to dryness under a stream of nitrogen. The methylated derivative was formed by adding 100 μL of 1:20 tetramethylammonium hydroxide:dimethylsulfoxide to the sample. After mixing and waiting for two to three minutes, 10 μL of methyl iodide was then added. This was followed, after a one minute wait, by the addition of 1 mL of iso-octane and transfer of the organic (top) layer to a clean tube. The sample was evaporated to dryness in a 60°C water bath with a stream of nitrogen, reconstituted with 200 μL of iso-octane and transferred to a GC vial with micro-insert. One or two μL of this solution was injected into the HP GC/MS operating in the SIM mode. Chromatography was performed with initial temperature at 80°C for one minute followed by 40°C/min ramp to 280°C. Ions monitored were 316 and 375 for the methylated deuterated internal standard and 313, 357 and 372 for methylated Carboxy-THC. Quantitation for Carboxy-THC was done using 313:316 peak area ratio.

Confirmation of methadone was carried out using either a methanolic extract of meconium or 5 mL of urine. Deuterated methadone (100 ng/mL) and 1 mL of 0.1 M phosphate buffer (pH 6.0) were added to the sample. After mixing, the buffered sample was then added to a Bond Elut Certify solid phase extraction column that had been preconditioned sequentially with methanol and phosphate buffer. The column was then washed sequentially with 1.0 M acetic acid and methanol. Methadone was eluted two mL of 2% ammonium hydroxide in ethyl acetate. The eluate was evaporated to dryness under a gentle stream of nitrogen, reconstituted with 200 μL of iso-octane and transferred to a GC vial with micro insert. One or two μL of this solution was injected into the HP GC/MS operating in the SIM mode. Chromatography was performed with initial temperature at 80°C for one minute followed by a 35°C/min ramp to 280°C. Ions monitored were 226 and 297 for the deuterated internal standard and 223, 294 and 295 for methadone. Quantitation was done using 294:297 peak area ratio.

Results and Discussion

Comparison of Maternal Urine and Meconium for Detection of Cocaine Metabolite

Of the 303 maternal urine specimens collected and tested (Table 1), 37 were positive for cocaine metabolite as benzoylecgonine for a positive rate of 12.2%. Of the 345 meconium specimens collected and tested (Table 2), 41 were positive for cocaine metabolite yielding a positive rate of 11.9%.

TABLE 1—*Maternal urine drug screen summary.*

	Cocaine metab Benzoylecgonine	THC Metab	Opiates	Methadone
Total maternal urines tested	303	299	300	300
Positive maternal urines	37	18	4	3
% Positive	12.2	6.0	1.3	1.0

Of the 37 positive maternal urine specimens, 24 meconium specimens were also positive. Ten maternal urine specimens had no corresponding meconium sample collected. One meconium sample had an interference when screened by EMIT on the Olympus. Two meconium specimens were negative.

Of the 41 positive meconium specimens, 24 maternal urine specimens were also positive. Ten meconium specimens had no corresponding maternal urine samples collected. Two maternal urine specimens had borderline screening results that were not sent on for GC/MS confirmation. Five maternal urine specimens were negative.

From these results, only two meconium specimens were negative compared with corresponding positive maternal urine specimens. On the other hand, five maternal urine specimens were negative compared with corresponding positive meconium specimens. It appears that meconium may be more reliable than maternal urine for detection of intrauterine cocaine exposure.

Comparison of Newborn Urine and Meconium for Detection of Cocaine Metabolite

Of the 351 newborn urine samples collected and tested (Table 3), 42 were positive for cocaine metabolite for a positive rate of 12.0%. A total of 345 meconium specimens were collected and tested. A total of 41 of these were positive for cocaine metabolite for a positive rate of 11.9%.

Of the 42 positive newborn urine specimens, 30 meconium specimens were also positive. Ten newborn urine samples had no corresponding meconium. Two meconium specimens were negative. One of these negative meconium samples had a corresponding maternal urine sample with benzoylecgonine concentration of 88 ng/mL and newborn urine sample benzoylecgonine concentration of 170 ng/mL.

Of the 41 positive meconium specimens, 31 newborn urine samples were also positive. Three meconium specimens had no corresponding newborn urine collected. Five newborn urine specimens were negative. On reinspection, two additional newborn urine samples were borderline but were not sent on for confirmation by GC/MS.

As was the case when comparing with maternal urines, meconium also appears to be a more useful sample than newborn urine for detection of cocaine metabolite.

TABLE 2—*Meconium drug screen summary.*

	Cocaine metab Benzoylecgonine	THC Metab	Opiates	Methadone
Meconiums tested	345	327	344	344
Positive meconiums	41	0	2	2
% Positive	11.9	0	0.6	0.6

TABLE 3—*Neonatal urine drug screen summary.*

	Cocaine metab Benzoylecgonine	THC Metab	Opiates	Methadone
Total newborn urines tested	351	350	350	350
Positive newborn urines	42	0	5	2
% Positive	12.0	0	1.4	0.6

Comparison of Maternal Urine and Newborn Urine for Detection of Cocaine Metabolite

Of the 303 maternal urine specimens tested, 37 were positive for cocaine metabolite. Forty two of the 251 newborn urine samples tested were positive. Of the 37 positive maternal urine specimens, 29 newborn urine samples were also positive. Six maternal urine specimens had no corresponding newborn urine collected. One newborn urine sample had a borderline EMIT result that was not sent on for GC/MS confirmation. One newborn urine specimen was negative.

Of the 42 positive newborn urine specimens, 29 maternal urine samples were also positive. Ten newborn urine specimens had no corresponding maternal urine collected. Two maternal urine samples were borderline on reinspection and were not sent on for GC/MS confirmation. One maternal urine specimen was negative.

From these results, it appears that the maternal urine and newborn urine have approximately the same reliability for detection of prenatal cocaine exposure.

Detection of THC Metabolite

THC Metabolite (Carboxy-THC) was detected in 18 of 299 maternal urine specimens tested for a positive rate of 6.0% (Table 1). No positive results were obtained from the 350 neonatal urine samples or the 327 meconium specimens that were tested (Tables 2 and 3). Fourteen meconium samples demonstrated activity above the negative control but did not confirm by GC/MS. In our study, maternal urine clearly appears to be the only specimen useful for detection of THC metabolite.

Detection of Opiates

Specimens were screened by EMIT and then confirmed for codeine and morphine by GC/MS. Codeine and morphine were both positive on four out of 300 maternal urine samples tested (Table 1) for a positive rate of 1.3%. Five out of 350 newborn urine specimens tested were positive for opiates for a positive rate of 1.4% (Table 3). Of the five maternal urine samples positive for both codeine and morphine, three of the newborn urine samples were positive for morphine only. Two of the positive maternal urine specimens had corresponding newborn urine samples that were negative and two of the positive newborn urine specimens had no corresponding maternal urines.

Two out of 344 meconium specimens tested were positive for opiates (Table 2) for a positive rate of 0.6%. In both cases, analysis by GC/MS confirmed morphine only. One of these positive meconium samples had a corresponding maternal urine sample positive for codeine and morphine and a corresponding neonatal urine sample positive for morphine. The other positive meconium specimen had a neonatal urine specimen positive for codeine and morphine with no corresponding maternal urine specimen. It does not appear that meconium is as useful as either maternal or neonatal urine for detection of codeine and morphine.

Detection of Methadone

Specimens were screened by EMIT and then confirmed for methadone by GC/MS. Methadone was positive for three of 300 maternal urine specimens tested for positive rate of 1.0% (Table 1). Two out of 350 newborn urine samples tested were positive for methadone for a positive rate of 0.6% (Table 3). Two out of 344 meconium specimens tested were positive for a positive rate of 0.6% (Table 2). With the low incidence of methadone use in the study, it does not appear that testing of meconium is advantageous. However one of the positive meconium samples did have a corresponding neonatal urine that was negative.

Comparison with Other Studies

Our study represents one of two large scale investigations reported to date in which GC/MS was used to confirm meconium drug screening results. The other study of Varley et al. [*19*] was recently presented in abstract form. Their method used an acetonitrile extraction of meconium, followed by solid phase extraction of meconium and derivatization of benzoylecgonine with PFPA. They found a positive rate of 5.3% and were able to confirm all meconiums which had a corresponding positive neonate urine. In accord with our study, they concluded that meconium offered the potential of identifying additional newborns who were not clinically suspected of cocaine exposure and whose urines tested negative.

The other previously published, large scale investigation of meconium drug analysis was done by Ostrea [*1*]. Their study used RIA screening only and reported 31% positive for cocaine, 21% positive for morphine and 12% positive for cannabinoid. This was considerably higher than our findings of 12% positive for cocaine, 0.6% positive for morphine and 0% positive for cannabinoid. Several factors may account for this. The populations studied were different, although both came from metropolitan areas with high incidences of drug use. Both studies avoided pre-selection by using specimens from a large number of consecutive births. A major difference was the cutoff used for screening. Ostrea's cutoffs for cocaine, morphine and THC were 15, 25 and 50 ng/mL respectively and were established by using two standard deviations above the mean from 19 drug free meconiums. In our study, any specimen having an activity of at least ten milliabsorbance units above the negative control was then confirmed by GC/MS when the quantity of specimen was sufficient to permit this. In addition, the matrix effects associated with RIA and EMIT would also differ, which might then influence the positive rates seen in the screening procedure.

Future Potential Use of Meconium for Drug Screening

It is evident from the large number of presentations at the most recent national AACC meeting [*19,20,22–24*] that there is a great deal of interest in the analysis of meconium for neonatal drug testing. In addition, Spiehler's article [*25*] gives a current, comprehensive review of recent studies using meconium. A number of studies [*1,2,20,24*] including ours have shown that meconium is the most useful specimen for the detection of prenatal cocaine exposure. While parent cocaine has been detected in meconium, virtually all forensic drug testing laboratories have an established method for benzoylecgonine confirmation. The presence of cocaine in the meconium of the neonate [*20*] serves as a reminder that the baby has been exposed to the pharmacologically active, parent drug in utero. To enhance sensitivity, testing of meconium in the future should use cutoffs for screening and GC/MS that are lower than those mandated in the forensic urine drug testing programs. Most laboratories will not have a problem with this, because, currently

standard methods use limits of quantitation at levels at least 50% below these mandated cutoffs. In the future, analysis of meconium hopefully will be viewed as an additional reliable test with the capacity to complement urine drug screening of the mother and newborn and to withstand legal challenges.

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