Mectest Cocaine Radioimmunoassay: (MCR)

Intended Use:

Mectest Cocaine Radioimmunoassay is a solid-phase ^{125}**I** radioimmunoassay (RIA) designed for the quantitative and qualitative measurement in meconium of benzoylecgonine, the principal metabolite of cocaine. It is intended strictly for in vitro use in the context of a program involving an established confirmatory test for cocaine and its principal metabolites.

The Mectest Cocaine Radioimmunoassay (MCR) kit assay provides only a preliminary analytical test result. A more specific, alternate, chemical method must be used in order to obtain a confirmed analytical result. Gas chromatography/mass spectrometry (GC/MS) is the preferred confirmatory method. Clinical consideration and professional judgment should be applied to any drug of abuse test result, particularly when preliminary positive results are used.

Catalog Numbers: (MCR)

The 100-tube kit contains not more than 10 microcuries (370 kilobecquerels) of radioactive ^{125}**I** benzoylecgonine.

Introduction:

Cocaine (benzoylmethylecgonine) can lose its methyl group through hydrolysis, and the benzoyl group through the action of pseudocholinesterase. Approximately 70% emerges in the urine over 48 hours, primarily as benzoylecgonine. In the fetus, the presence of benzoylecgonine in meconium is postulated to be secondary to fetal swallowing of amniotic fluid, which is partly fetal urine, and from the secretion of benzoylecgonine through the bile.

The Mectest Cocaine RIA is a solid-phase radioimmunoassay wherein ^{125}**I** benzoylecgonine competes for a fixed time with benzoylecgonine in the patient sample for sites on benzoylecgonine-specific antibody. The antibody is immobilized to the wall of a polypropylene tube; hence decanting the supernatant suffices to terminate the competition and to isolate the antibody-bound fraction of the radiolabeled benzoylecgonine. Counting the tube in a gamma counter then yields a number, which converts by way of a calibration curve to a measure of the benzoylecgonine present in the patient sample.

Procedure:

There is only one reagent to dispense, and a single two-hour incubation at room temperature. No centrifuge is required. Sample and tracer additions can be handled simultaneously, if desired, with the help of an automatic pipettor-diluter. The simplicity of the Mectest Cocaine RIA procedure makes it ideal for high-volume screening.

Separation: The coated-tube methodology offers significant advantages in reliability, as well as speed and convenience, since the tubes can be vigorously decanted, without loss of antibody-bound material. This results in a clean separation of bound from free, with negligible nonspecific binding.

Data Reduction:

Conventional RIA techniques of calculation and quality control are applicable. The assay has been optimized for linearity in a logit-log representation throughout the range of its calibrators. Moreover, the computation can be simplified by omitting the correction for nonspecific binding, without compromising results or quality control.

Calibration:

The kit is equipped with standards ranging from 100 to 5,400 ng/mL. The standards are supplied in liquid form, ready to use. We recommend that standard calibrators be diluted to levels at or near the cutoff concentration.

Counts:

The tracer has a high specific activity, with total counts of approximately 150,000 cpm at iodination. Maximum binding is approximately 30-35%.

Precision:

CV's are low and uniform, and no "end of run" effect has been observed in assays involving up to 200 tubes.

Specificity:

The antiserum is highly specific for benzoylecgonine, with very low crossreactivity to other non-class-related compounds that might be present in patient samples.

Accuracy:

Extensive experiments have shown that the assay is accurate over a broad spectrum of benzoylecgonine values. Its accuracy has been further verified in patient comparison studies against GC/MS.

Warning and Precautions:

For in vitro diagnostic use. Before opening the kit, review the paragraphs on safety printed on the inside front cover, as they relate to the safe handling and disposal of reagents containing radioactivity, human serum and sodium azide. Prepare all components at least 10 minutes prior to use.

Materials Supplied:

Initial Preparation

1. **Benzoylecgonine Antibody-coated tubes: (MCR1)**
100 polypropylene tubes coated with sheep antibodies to benzoylecgonine and packaged in zip-lock bags. The antiserum is highly specific for benzoylecgonine , with very low crossreactivity to other non-class-related compounds. Store refrigerated and protected from moisture, carefully resealing the bags after opening: stable at 2-8° C for at least one year from the date of manufacture.

2. **^{125}I Benzoylecgonine: (MCR2)**
One vial of lyophilized iodinated benzoylecgonine. Reconstitute each vial by adding a measured 110-mL of distilled water. Let stand for 10 minutes, then mix by gentle inversion. Store refrigerated: stable at 2-8° C for at least 30 days after reconstitution, or until the expiration date marked on the vial.

3. **Benzoylecgonine calibrators: (MCR3)**
One set of six vials labeled A through F, of benzoylecgonine calibrators. The calibrators are supplied in liquid, aqueous, form, ready to use. The zero calibrator, vial A, contains 5 mL, and the remaining calibrator vials B through F, each contains 2 mL. Store refrigerated: stable at 2-8° C for at least 30 days after opening. Freezing can extend the life of the calibrators. Aliquot if necessary to avoid repeated thawing and freezing. The calibrators in aqueous solution contain 0, 100, 300, 900, 2,700 and 5,400 nanograms of benzoylecgonine per milliliter (as the free base). Intermediate calibration points may be obtained by mixing calibrators in suitable proportions.

Materials Required But Not Provided

1. Benzoylecgonine meconium controls: Emulsify 0.5 g of drug free meconium in 5 mL of meconium solvent in the meconium processor. (See procedure below for meconium collection and processing). Add 25 microliters of benzoylecgonine calibrator (2700 ng/mL): final benzoylecgonine concentration is 13.4 ng/mL (meconium control 1). Emulsify another 0.5 g of drug free meconium in 5 mL of meconium solvent and add 150 microliters of benzoylecgonine calibrator (5400 ng/mL): final benzoylecgonine concentration is 157.3 ng/mL (meconium control 2). Process meconium controls 1 and 2 as below (see Meconium processing).

2. Gamma counter - compatible with standard 12x75 mm tubes

3. Vortex mixer

Note: Additional calibrators can be purchased through Mectest Corporation.

Reagent Preparation:

1. Distilled or deionized water

2. Graduated cylinder: 110 mL

Radioimmunoassay:

1. Plain 12x75 mm polypropylene tubes - for use as NSB tubes.

2. Micropipets: 25 uL, 150 µL and 1000 µL for the 1.0 mL reagent addition, a reliable repeating dispenser (Nichiryo or equivalent) are also suitable. With an automatic pipetter-diluter, sample and reagent additions may be handled simultaneously. A disposable tip, air-displacement pipet (Nichiryo, MLA or equivalent) is recommended for the 25 µL sample addition, to minimize the risk of carry-over.

3. Foam decanting rack - available from Diagnostic Products Corporation, 5700 West 96th Street, Los Angeles, CA 90045.

Procedure for the Preparation & Analysis of Cocaine in Meconium

A. Meconium Collection:

1. Mix meconium in infant's diaper before sampling. Pooling of meconium from several diapers before sampling will improve the detection rate of drugs in meconium (see below).
2. Unscrew cap of MECTEST meconium processor. Set tube in a rack (Do not spill reagent).
3. Use scoop attached to the cap to obtain 0.5 g of meconium (approximately one large, scoopful of meconium).
4. Place cap and scoop containing meconium back into the MECTEST processor.
5. Screw cap tightly.

Note: If meconium is sent to an outside laboratory for analysis, meconium should be vortexed and emulsified in meconium solvent (see Meconium processing, step 1) prior to mailing.

B. Meconium Processing:

1. Vortex MECTEST processor, with scoop acting as a stirrer, until meconium is well dispersed in the solvent. (To test, lay tube at its side - globs of meconium should not be seen).
2. Detach scoop from cap and discard scoop.
3. Recap tube and centrifuge at 4600 rpm (3000 g) for 30 minutes.
4. Collect supernate and transfer 1 mL into the ultrafilter provided in the kit. (Save remaining supernate for future use).
5. Centrifuge at 4600 rpm (3000 g) for 30 min. Let stand for 10 min. to avoid overheating. Repeat centrifugation at 4600 rpm for another 30 min.
6. Collect total ultrafiltrate (approximately 250 microliters) for drug analysis.

Note: Meconium with benzoylecgonine concentrations greater than that of the highest calibrator in the assay should be diluted with the kit's zero calibrator to bring the sample within the range of the calibrators.

C. Radioimmunoassay:

(All components must be at normal room temperature prior to use)

1. Set up and label as many tubes as are required for the Total, Calibration Standards (A-G), meconium ultrafiltrate (unknown specimens) and meconium controls, numbered "1" and "2" to be assayed.

Calibrators	ng/mL
A(MB)	0
B Diluted	25*
B	100
C	300
D	900
E	2700
F	5400

* Calibrator at 100 ng/mL should be diluted with 0.1M phosphate buffer (pH=7.0) to achieve this concentration.

2. Add 25 microliters each of the Calibrators, meconium ultrafiltrates and Controls to their appropriate test tubes. Pipet directly to the bottom of the tube. (Samples with high concentrations of benzoylecgonine should be diluted using the kit's zero calibrator). Run the total, calibrators, unknown and controls, at least, in duplicate.

3. Add 1.0 mL of ^{125}I Benzoylecgonine (Red) to every tube. Vortex. Laboratories equipped with a reliable pipettor-diluter may handle steps 2 and 3 simultaneously. No more than ten minutes should elapse during the dispensing of the tracer.

4. Incubate tubes at room temperature for 2 hours.

5. Set aside the Total tubes and decant the rest of the tubes. Removing all visible moisture will greatly enhance precision. Using a foam decanting rack, decant the contents of all tubes (except the T tubes) and allow them to drain for 2 or 3 minutes. Then strike the tubes sharply on absorbent paper to shake off all residual droplets.

6. Count for 1 minute in a gamma counter,

D. Quantitative Analysis:

1. To calculate benzoylecgonine concentrations from a logit-log representation of the calibration curve, first calculate for each pair of tubes the average NSB-corrected counts per minute:

Net Counts = Average CPM - Average NSB CPM

Then determine the binding of each pair of tubes as a percent of maximum binding (MB), with the NSB-corrected counts of the A tubes taken as 100%:

$$\text{Percent Bound} = \frac{\text{Net Counts}}{\text{Net MB Counts}} \times 100$$

The calculation can be simplified by omitting the correction for nonspecific binding (NSB): samples within range of the calibrators yield virtually the same results when Percent Bound is calculated directly from Average CPM. Using the logit-log graph paper provided with the kit, plot Percent Bound on the vertical axis against Concentration on the horizontal axis for each of the calibrators B through G, and draw a straight line approximating the path of these five points. Benzoylecgonine concentrations for the unknowns may then be estimated from the line by interpolation. Although other approaches are acceptable, data reduction by the logit-log method just described has certain advantages in this context - for example, in allowing easier recognition of deviant calibration points - since the procedure has been optimized for linearity in that representation.

Example: The figures tabulated below are for illustration only and should not be used to calculate results from another assay.

Tube	Duplicate CPM	Average CPM	Net CPM	Percent Bound	Benzo-ylecgonine (ng/mL)
T	143,415				
	142,116	142,967			
NSB	844				
	868	856	0		
A(MB)	46,267				
	46,283	46,275	45,419	100.0 %	0
B Dil	34,552				
	33,478	34,015	33,159	73.0%	25
B	32,838				
	32,394	32,616	31,760	69.9%	100
C	26,372				
	26,946	26,659	25,803	56.8%	300
D	18,428				
	19,060	18,744	17,888	39.4%	900
E	11,869				
	11,803	11,836	10,980	24.2%	2,700
F	9,116				
	8,670	8,893	8,037	17.7%	5,400
Unknowns					
X1	25,768				
	25,546	25,657	24,801	54.6%	325
X2	15,792				
	15,600	15,696	14,840	32.7%	1,450

Quality Control Parameters:

T = 142,967 cpm.
%NSB = 0.6%
%MB = 32%
20% Intercept = 4,400 ng/mL
50% Intercept = 440 ng/mL
80%Intercept = 45 ng/mL

E. Reporting of Results

1 Negative test results:

Cocaine concentrations in meconium, which are below the cut off concentration, are reported as:

Negative for cocaine
Cut off concentration:

(minimum drug detectable) = 7.62 ng/mL

Warning:
A negative result does not eliminate the possibility of consumption of illicit drugs by the mother. The formation of meconium starts at the 12th week of gestation. Thus, illicit drug use by the mother during the first trimester of pregnancy may not result in a positive meconium drug test. Similarly, meconium samples may not all be positive for drugs if the mother has only been an episodic user of drugs. Thus, pooling of meconium obtained from a number of diapers will increase the likelihood of a positive test. The results of the meconium drug test should also be correlated to the maternal history and to toxicological tests that have been done on the mother. When meconium is used in any other systems/methods for the detection of drugs of abuse, the user must be aware that the performance characteristics of such systems/methods have not been determined by the manufacturer nor have been FDA cleared. Likewise, the concentrations of the drug of abuse in meconium using such systems/methods have not been correlated with the dose of the drug of abuse consumed by the mother nor with the clinical picture in the neonate.

2) Positive test results:
Cocaine concentrations in meconium at or greater than the recommended cut off concentrations are reported as:

Presumptive positive for cocaine
Cut off concentration:
(minimum drug detectable) = 7.62 ng/mL

Warning: These are only preliminary test results. All positive tests should be confirmed by more specific methods. Gas chromatography/mass spectrometry or GC/MS is the confirmatory method of choice.

Performance Characteristics

I. Sensitivity
The sensitivity of the MECTEST Cocaine Radioimmunoassay was determined by spiking meconium with different amounts of benzoylecgonine and analyzing the different benzoylecgonine concentrations by radioimmunoassay. A stock solution (10,000 ng/mL) of the benzoylecgonine was prepared in methanol. The concentration of the stock solution was analyzed by radioimmunoassay and the amount of drug spiked into the meconium suspension was calculated based on the analyzed concentration of the stock solution. Spiked meconium was prepared as follows: 0.5 g of drug free meconium was suspended in 5 mL of solvent in the MECTEST processor. The mixture was vortexed for 5 minutes. Known amounts of benzoylecgonine from the stock solution were added to the meconium suspension to achieve 11 drug concentration levels ranging from 0 to 207 ng/mL. The spiked meconium was processed using MECTEST and the ultrafiltrate was analyzed for cocaine (observed concentration) by MECTEST Cocaine Radioimmunoassay.

Results:
The observed and expected concentrations of cocaine (benzoylecgonine) in meconium were plotted in a linear regression model which showed the following results: correlation coefficient (r) = 0.988 ($p<0.0001$), goodness of fit (r^2) = 0.976, constant = -4.72 ng/mL and slope of the regression line = 0.988. The minimum detectable (cutoff) concentration for cocaine = 7.62 ng/mL (derived from the intercept of the regression line at the 95% confidence limit).

II. Specificity
Cross reactivity: Meconium was emulsified using the MECTEST Processor and tested for the presence of endogenous compounds. Meconium was also spiked with cocaine, morphine and cannabinoid at concentrations ranging from 0 to 423 ng/mL, as well as with the following drugs prepared at concentrations of 100,000 ng/mL, namely: acetaminophen, phenobarbital, acetylsalicylic acid, propoxyphene, pentazocine, chlorpromazine, ibuprofen, meperidine, diazepam, lidocaine and caffeine.

Meconium contained endogenous amounts of bilirubin (60.23 ± 2.76 micrograms/gm meconium), blood (0 to +++ hemoglobin by qualitative guiac test) and protein (32.89 ± 12.36 mg/gm meconium) which did not interfere in the recovery of cocaine in meconium. Similarly, cross-reaction between cocaine, opiate or cannabinoid at the concentrations used was not observed. Recovery rate was 104.5 ± 14.1% for cocaine. There was 0% to 0.2% cross reactivity of cocaine to the following drugs which were prepared at concentrations of 100,000 ng/mL: acetaminophen, phenobarbital, acetylsalicylic acid, propoxyphene, pentazocine, chlorpromazene, ibuprofen, meperidine, diazepam, lidocaine and caffeine.

Cross reactivity between various cocaine metabolites:

Drug	ng/mL	Cross reactivity(%)
L-benzoylecgonine	300	104
L-cocaine	50	7259
L-ecgonine methyl ester	5000	1.3
L-ecgonine	5000	5.6
L-benzoylnorecgonine	5000	1.9
L-norcocaine	50	63.5
D-cocaine	5000	7.4
D-pseudococaine	5000	1.0
L-pseudococaine	5000	0.1
L-pseudoecgonine methyl ester	5000	0.3
D-pseudoecgonine methyl ester	5000	0.3

III. Precision

1. Interassay precision:

Known amounts of cocaine were spiked into 5 meconium samples (0.5 g per sample) to give a drug concentration in each sample of 200 ng/mL. Each sample was processed individually and analyzed for cocaine. The interassay coefficient of variability (CV) for cocaine was 8.327% .

2. Intra-assay precision:

To determine intra-assay precision, triplicate analysis for cocaine were done on 8 meconium samples. A coefficient of variability was obtained for each triplicate analysis and a mean coefficient of variability for the 8 samples was calculated. The mean (sd) coefficient of variability was 5.9 ± 3.9% for cocaine.

To compare "within sample" drug concentration, meconium from 2 infants were sampled at two sites per specimen and tested for cocaine by radioimmunoassay. The results (see below) showed varying concentration of drugs per site within samples. This indicates that drugs are unevenly distributed in meconium. Thus, for appropriate sampling, meconium has to be mixed well before an aliquot is taken.

Comparison of cocaine concentrations in meconium at 2 sampling sites (sites A and B)

Cocaine concentration (ng/mL)		
	Site A	Site B
Specimen 1	518.88	337.73
Specimen 2	638.42	561.75

IV. Drug Stability in Meconium

The stability of cocaine in meconium was tested under the following conditions: (1) at room temperature for 24 hours, (2) meconium, emulsified in MECTEST solvent for 72 hours at room temperature and (3) at -15^{o} C for at least 9 months.

1. Meconium allowed to stand at room temperature for 24 hours resulted in a 25% decrease in cocaine concentration. Thus, meconium should be sampled and processed as soon as possible after its excretion by the infant to prevent loss of cocaine.

Effect on cocaine concentration if meconium is allowed to stand at room temperature for 24 hours

Meconium cocaine concentration (ng/mL)			
	0 hour	24 hours	% change
Sample 1	518.88	350.24	-32.5
Sample 2	337.73	270.43	-19.9
Sample 3	638.42	463.51	-27.4
Sample 4	561.76	378.17	-32.7

2. Meconium emulsified in MECTEST solvent and kept at room temperature for 72 hours did not show a decrease in its concentration of cocaine. Thus, cocaine in meconium is stable for 3 days, if suspended in MECTEST solvent.

Effect on meconium cocaine concentration if meconium is emulsified in MECTEST solvent and kept at room temperature for 72 hours.

Meconium cocaine concentration (ng/mL)			
	0 hour	72 hours	% change
Sample 1	518.88	527.12	+1.6
Sample 2	337.73	353.73	+4.7
Sample 3	638.42	684.01	+7.1
Sample 4	561.76	618.81	+10.2

3. The effect of freezing meconium at -15 ^{o} C on cocaine concentration is shown below. At -15 ^{o} C, cocaine is stable in meconium for at least 9 months.

Interval between		Cocaine (ng/mL)	
Sample	test (days)	Original conc	Conc after freezing
1	322	13611	16809
2	322	16122	21249
3	322	2683	6246
4	170	6629	9472
5	170	10223	9608
6	170	20605	16952
7	170	1475	2286
8	109	3410	2802
9	120	19581	17903
10	109	16566	19881
11	109	21783	18612
12	109	17011	13487
13	109	0	0

V. Clinical Study

Fifty meconium samples from in utero drug exposed and control infants were analyzed for cocaine by MECTEST Cocaine Radioimmunoassay and gas chromatography/ mass spectrometry (GC/MS) [16] . The table shows agreement between the RIA and GC/MS results.

Sample	RIA (ng/mL)	GC/MS	Sample	RIA (ng/mL)	GC/MS
1	16809	+	26	299	+
2	45.29	+	27	6429	+
3	27.88	+	28	5568	+
4	9472	+	29	1342	+
5	9608	+	30	96	+
6	25.56	+	31	0	-
7	77.77	+	32	1229	+
8	2802	+	33	1927	+
9	17903	+	34	1507	+
10	48.92	+	35	7474	+
11	18612	+	36	3409	+
12	13487	+	37	3058	+
13	2113	+	38	0	-
14	1166	+	39	0	-
15	0	-	40	3426	+
16	0	-	41	10222	+
17	32920	+	42	51	+
18	25403	+	43	0	-
19	42836	+	44	0	-
20	43143	+	45	0	-
21	28171	+	46	16122	+
22	22909	+	47	347	+
23	21303	+	48	5753	+
24	8699	+	49	0	-
25	0	-	50	16565	+

VI. Effect of Carryover

Patient samples may occasionally have very high concentrations of cocaine. It is suggested that routine precautions be taken, e.g., employing a fresh pipet tip for each sample, to avoid carryover contamination.

VII. Limitations

Based on a review of the literature, the following may cause false positive reactions:

1. Maternal ingestion of food or drinks containing coca products (such as herbal tea).
2. Passive maternal inhalation of cocaine.
3. Technical or procedural errors.

VIII. Quality Control

1. Record Keeping:

It is good laboratory practice to record for each assay, the lot numbers and reconstitution dates of the components used.

2. Sample Handling:

It is good laboratory policy to maintain accurate chain of custody of specimens. The instructions for the proper collection, handling and storage of samples should be followed.

Criteria for non acceptance of specimen, include:

a) Improperly identified specimen,
b) Leakage of specimen container,
c) Broken container.

The instructions for handling and storing patient samples and components should be carefully observed. Dilute high patient samples with the kit's zero calibrator prior to assay. All samples, including the calibrators and controls, should be assayed in duplicate. It is good laboratory practice to use a disposable-tip micro-pipet, changing the tip between samples, in order to avoid carry-over contamination. Pairs of control tubes may be spaced throughout the assay to help verify the absence of significant drift. Inspect the results for agreement within tube pairs, and take care to avoid carryover from sample to sample.

3. Controls:

We recommend that in accordance with guidelines set by the National Institute on Drug Abuse, controls should be assayed at or near the cutoff concentrations and the results charted from day to day. (J.0. Westgard et al, "Multi-rule chart for quality control" Clinical Chemistry 27 (1981) 493-501. See also Scandinavian Journal of Clinical and Laboratory Investigation 44 (1984) Suppl 171 and 172. Repeat samples are a valuable additional tool for monitoring interassay precision.

4. Data Reduction:

It is good practice to construct a graph of the calibration curve as a visual check on the appropriateness of the transformation used, even where the calculation of results is handled by computer. See further S.E. Davis et al, "Radioimmunoassay data processing with a small programmable calculator" Journal of Immunoassay 1(1980) 15-25; and R.A. Dudley et al, "Guidelines for immunoassay data reduction" Clinical Chemistry 31 (1985) 1264-71.

Q. C. Parameters: We recommend keeping track of the following performance measures.

Quantitative Procedure
T = Total Counts (as counts per minute)

$$\%NSB = 100 \times \frac{\text{Average NSB Counts}}{\text{Total Counts}}$$

$$\%MB = 100 \times \frac{\text{Average MB Counts - Average NSB Counts}}{\text{Total Counts}}$$

IX. Clinical Applications:

The analysis of drugs and their metabolites in meconium is a new and sensitive method for identifying infants who have been exposed to drugs in utero .[1-2] Meconium represents the first series of green stools of the newborn infant which are passed within a few days after birth. The concept behind meconium testing was based on initial research in animals that showed a high concentration of the drugs which the pregnant animal was exposed to, were present in the meconium of their fetuses. [2-5] Drugs that the fetus is exposed to during pregnancy are metabolized by its liver into water-soluble metabolites and excreted into the bile or urine. It is postulated that drug deposition in meconium occurs either through bile secretion or through swallowing by the fetus of its urine via the amniotic fluid. Clinical studies in humans have validated meconium analysis as a sensitive drug screen in the newborn infant. [6-9] The initial clinical study compared drug detection in 20 infants of drug dependent mothers by meconium and urine analysis[2]. Whereas all meconium samples contained either cocaine, opiate or cannabinoid, only 37% of the urine tested was positive for these drugs. Subsequent studies have corroborated the sensitivity of meconium drug testing. In one study, meconium was analyzed for cocaine, morphine, codeine and marijuana from 28 neonates born to women suspected of drug abuse. [9] In each case, testing of urine from the mother, the infant or both were done because of suspected maternal drug abuse. Compared with the combination of maternal and newborn urine testing, meconium testing had an 82% positive predictive value and a 91% negative predictive value. The authors further added that the collection of meconium was simpler and more reliable than collection of urine and that the testing of meconium was easily incorporated into routine procedures at a busy commercial laboratory. In another study, a comparison of the sensitivity of meconium and urine analyses for drugs in detecting gestational exposure to cocaine was studied. [8] The infants were born to 59 women who were interviewed to determine their use of cocaine during pregnancy. Radioimmunoassay and gas chromatography of meconium were more sensitive than immunoassay of urine ($p<0.02$). Urine immunoassay failed to identify 60% of cocaine exposed infants. The largest clinical study using meconium drug testing was a drug prevalence study conducted in a large, high risk, obstetric population[6]. The superiority of meconium testing over maternal history was demonstrated. A fourfold (44.3% vs 11.1%) higher incidence of drug exposure was found among 3010 infants tested by meconium analysis as compared to maternal history. The meconium drug test has also been adapted for mass drug screening of newborn infants [10] and selection criteria for routine testing of infants have been formulated. [11]

Recently, other studies have been published illustrating the clinical application of the meconium drug test. The meconium test was used to prospectively screen for drugs (opiates, cocaine and cannabinoids) every infant who was admitted to the neonatal intensive care unit of a high-risk perinatal center for a 3-month period. [12] Of the 82 infants tested, 41 or 50% were positive for drugs: 36 (44%) positive for cocaine, 9 (11%) positive for opiates and none for cannabinoid. The total cost for the care of these infants was $1,223,750. The authors concluded that there is a high prevalence of drug exposure in infants admitted to the neonatal intensive care and that the morbidity, mortality and medical cost, associated with drugs, are significant. A biologic marker of fetal exposure to nicotine in passive and active maternal smoking has also been determined by meconium analysis. [13] Nicotine metabolites (cotinine and trans 3'-hydroxycotinine) were detected in meconium at concentrations proportional to the degree of maternal active and passive smoking. Furthermore, in utero exposure to tobacco smoke in infants of passive smokers was as high as among infants whose mothers actively smoked less than 1 pack per day during pregnancy. Lastly, a comparative methodological study was done to detect in utero cocaine exposure in infants. Maternal history was compared with various assays in meconium, Maternal urine and infant's urine, using GC/MS, EMIT, ADx and DPC radioimmunoassay. The authors found meconium to be superior to either maternal or infant urine in detecting in utero cocaine exposure, although the need for concomitant maternal histories in some cases was emphasized. [14]

In summary, meconium drug testing is ideal in the newborn period for several reasons: (i) the test is highly sensitive and specific, (ii) the test can be performed using common laboratory techniques for purposes of mass screening and with capabilities for GC/MS confirmation, (iii) collection of meconium is easy and non invasive, (iv) analysis of serial meconium can reflect the type, chronology and amount of in utero drug exposure of the infant[15] and (v) drugs in meconium are present up to the third day after birth; thus late testing of the infant for drugs is possible. Meconium drug testing has therefore become a useful tool for clinical and research needs.

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