Mectest Opiate Radioimmunoassay (MOR)

Intended Use:
Mectest Opiate Radioimmunoassay is a solid-phase ^{125}**I** radioimmunoassay (RIA) designed as a screen for the semiquantitative analysis of opiates in meconium. It is intended strictly for in vitro diagnostic use.

Catalog Numbers: MOR (100 tubes)
The 100-tube kit contains not more than 10 microcuries (370 kilbecquerels) of radioactive ^{125}**I** morphine.

Introduction:
The Mectest Opiate Radioimmunoassay is a solid-phase radioimmunoassay wherein ^{125}**I**-labeled morphine competes for a fixed time with opiates extracted from meconium for antibody sites. 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 morphine, which is then counted in a gamma counter. A comparison of the counts to a standard curve yields a measure of the opiate present in the sample, expressed as nanograms of morphine-3-glucuronide per milliliter (ng/mL).

Procedure:
All components are supplied in liquid form, ready-to-use. There is only one reagent to dispense and a single one-hour incubation. 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 procedure makes it ideal for high-volume testing.

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 having morphine-3-glucuronide values ranging from 25 to 1000 ng/mL.

Counts:
The tracer has a high specific activity, with total counts of approximately 150,000 cpm at iodination. Maximum binding is approximately 60%.

Precision:
CV’s are low and uniform, and no "end of run" effects has been observed in assays involving as many as 200 tubes.

Specificity:
The rabbit antiserum is broadly specific for opiates with very low crossreactivity to other non-related compounds that might be present in meconium.

Accuracy:
Extensive experiments have shown that the assay is accurate over a broad spectrum of values.

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. Opiate antibody- coated tubes: (MOR1)
100 polypropylene tubes coated with rabbit antibodies broadly specific for opiates with very low crossreactivity to other non-related compounds. The tubes are packaged in zip-lock bags. Store refrigerated and protected from moisture, carefully resealing the bags after opening: stable at 2-8 ^{o} C for one year from the date of manufacture.

2. ^{125}I Morphine: (MOR2)
One vial of lyophilized iodinated morphine, with azide as a preservative. Reconstitute each vial by adding a measured 110 mL distilled water. Let stand for 10 minutes, then mix by gentle inversion. Store refrigerated: stable at 2-8 ^{o} C for at least 30 days after reconstitution, or until the expiration date marked on the vial.

3. Opiate calibrators: (MOR3)
One set of eight vials labeled A through F (F1, F2 & F3), of morphine-3-glucuronide calibrators. The zero calibrators are supplied in liquid, aqueous form, ready to use. The calibrator, vial A, contains 2 mL, while each of the remaining calibrator vials B through F contains 1 mL. Store refrigerated: stable at 2-8 ^{o} C for at least 30 days after opening. Freezing may extend the life of the calibrators. Aliquot if necessary to avoid repeated freezing and thawing.

The calibrators contain respectively 0, 25, 75, 150, 300 and 1000 nanograms of morphine-3-glucuronide per milliliter. Intermediate calibration points may be obtained by mixing calibrators in suitable proportions.

Materials Required But Not Provided:

1. Opiate meconium controls: Emulsify 0.5 g of meconium from drug free infants in 5 mL of meconium solvent in the meconium processor. Add 200 microliters of opiate calibrator (1000 ng/mL) to produce an opiate concentration of 38.5 ng/mL (meconium control 1). Emulsify another 0.5 g of control (drug free) meconium in 5 mL of meconium solvent and add 1 mL of opiate calibrator (1000 ng/mL) to produce an opiate concentration of 166.7 ng/mL (meconium control 2). Process both meconium controls as below (see Meconium processing).

2. Gamma counter -compatible with standard 12x75 mm tubes.
3. Vortex mixer.
4. Centrifuge capable of at least 1500 g.

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 µL, 100 µL and 1000 µL for the 1.0 mL reagent addition, a reliable repeating dispenser (Nichiryo or equivalent) is also suitable. With the help of an automatic pipettor-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 carryover.
3. Foam decanting rack, available from Diagnostic Products Corporation, 5700 West 96th Street, Los Angeles, CA. 90045

Procedure for the Preparation and Analysis of Opiates 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 an ultrafilter provided in the kit. Save the remaining supernate for future use.
5. Centrifuge at 4600 rpm (3000 g) for 30 min. Let stand for 10 min. to prevent overheating. Repeat centrifugation at 4600 rpm for another 30 min.
6. Collect total ultrafiltrate (approximately 250 microliters) for drug analysis.

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

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-F), meconium ultrafiltrate (unknown specimens) and meconium controls, numbered "1" and "2" to be assayed.

Calibrators	ng/mL
A(MB)	0
B	25
C	75
D	150
E	300
F	1000

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

3. Add 1.0 mL of ^{125}I Morphine to every tube. Vortex. Laboratories equipped with a reliable pipettor-diluter may handle steps 2 and 3 simultaneously. No more than 10 min. should elapse during the dispensing of the tracer.

4. Incubate tubes at room temperature for 1 hour.

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 opiate concentrations in terms of morphine 3-glucuronide 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 F, and draw a straight line approximating the path of these five points. Opiate 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 table below is for illustration only and should not be used to calculate results from another assay.

Tube	Duplicate CPM	Average CPM	Net CPM	Percent Bound	Opiate* (ng/mL)
T	108,789				
	109,985	109,387			
NSB	528				
	576	552	0		
A(MB)	60,748				
	62,718	61,733	61,181	100 %	0
B	50,411				
	51,623	51,017	50,465	82.5%	25
C	43,316				
	44,212	43,764	43,212	70.6%	75
D	35,249				
	35,087	35,168	34,616	56.6%	150
E	24,946				
	26,367	25,657	25,105	41.0%	300
F	13,075				
	12,682	12,879	12,327	20.1%	1000
Unknowns					
X1	48,596				
	48,277	48,437	47,885	77.6%	40
X2	25,950				
	26,644	26,297	25,745	41.7%	288
X3	18,005				
	18,128	18,067	17,515	28.4%	602

* as morphine-3-glucuronide

Quality Control Parameters:

T = 109,387 cpm.
%NSB = 0.1%.
%MB = 56%
20% Intercept = 1081 ng/mL
50% Intercept = 194 ng/mL
80% Intercept = 35 ng/mL

E. Reporting of Results

1. **Negative test:** Opiate concentrations which are below the cut off concentration are reported as:

Negative for opiate
Cutoff concentration
(minimum drug detectable) = 27.82 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 concentration 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:** Opiate concentrations at or greater than the cut off concentration are reported as:

Presumptive positive for opiate
Cutoff concentration
(minimum drug detectable) = 27.82 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 MECTEST Opiate Radioimmunoassay was determined by spiking meconium with different amounts of morphine and analyzing the morphine concentrations by the radioimmunoassay. A stock solution (10,000 ng/mL) of morphine 3 glucuronide was prepared in methanol. The concentration of the morphine stock solution was analyzed by radioimmunoassay and the amount of each drug spiked into the meconium suspension was calculated based on the analyzed concentration of the stock solution. The 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 morphine 3 glucuronide standards were added to meconium to achieve 13 drug concentration levels ranging from 0 to 423 ng/mL. The ultrafiltrate was analyzed for morphine (observed concentration) by MECTEST Opiate Radioimmunoassay.

Results:

The observed and expected concentrations of morphine 3 glucuronide in meconium were plotted in a linear regression model which showed the following results: correlation coefficient (r) =0.994 ($p<0.0001$), goodness of fit (r^2) = 0.989, constant =14.95 ng/mL and slope of the regression line =0.697. The minimum detectable (cutoff) concentration for morphine = 27.82 ng/mL (derived from the intercept at the 95% confidence limit of the regression line).

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 the following drugs, which were 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 micrograms/gm meconium) which did not interfere in the recovery of morphine in meconium. Similarly, cross reaction between cocaine, opiate or cannabinoid at the concentrations used, was not observed. Recovery rate for morphine was 135.6 ± 9.6%. There was 0% to 0.2% cross reactivity of morphine to the following drugs which were prepared at concentrations of 100,000 ng/mL: acetaminophen, phenobarbital, acetylsalicylic acid,, propoxyphene, pentazocine, chlorpromazine, ibuprofen, meperidine, diazepam, lidocaine and caffeine.

The cross reactivity between the various related opiates are shown in the table:

Cross reactivity between various opiate metabolites:			
Compound	ng/mL added	Apparent conc ng/mL*	Crossreactivity(%)
Morphine-3-glucuronide			(100)
Ethylmorphine	10	691	6910
Morphine	1	44	4400
	10	602	6020
Codeine	1	50	5000
Dihydrocodeine	10	28	280
	100	223	223
Normorphine	10	20	200
	100	126	126
Hydromorphone	100	153	153
	1,000	>1,000	>100
Morphine-6-	10	8	80
glucuronide	100	11	11
	1,000	34	3
	10,000	424	4
Oxycodone	10	6	63
	100	12	12
	1,000	43	4
	10,000	285	3
Meperidine	1,000	9	0.9
	10,000	11	0.1
	100,000	6	0.006
Fentanyl	100,000	26	0.03
Buprenorphine	100,000	ND	0.0
Methadone	100,000	ND	0.0

*as morphine-3-glucuronide

III. Precision

1. Interassay precision: Known amounts of morphine were spiked into 5 meconium samples (0.5 g per sample) to give a morphine concentration in each sample of 200 ng/mL. Each sample was processed individually and analyzed for morphine by radioimmunoassay. The interassay coefficient of variability (CV) for morphine was 1.053%.

2. Intra-assay precision : To determine intra-assay precision, triplicate analyses for morphine were done on 8 meconium samples. A coefficient of variability was calculated for each triplicate analysis and a mean coefficient of variability was derived for the 8 samples. The mean (sd) coefficient of variability for morphine on the 8 samples was 4.5 ± 1.3%.

To compare "within sample" drug concentration, meconium from 2 infants were sampled at two sites per specimen and tested for morphine by radioimmunoassay. The results (see below) showed varying concentrations 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 opiate concentration at 2 sampling sites

Opiate concentration (ng/mL)		
	Site A	Site B
Specimen 1	160.61	119.44
Specimen 2	321.75	285.04

IV. Drug Stability In Meconium

Stability of morphine 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) frozen at - 15^{o} C for up to 9 months.

1. Meconium allowed to stand at room temperature for 24 hours resulted in a mean increase in morphine concentration by 62% (see below). The increase in morphine concentration represents the hydrolysis of morphine glucuronide to morphine due to the high beta glucuronidase activity of meconium and the higher sensitivity (40x) of radioimmunoassay for morphine compared to its glucuronide. Thus, meconium should be sampled and processed as soon as possible.

Effect on morphine concentrations if meconium is allowed to stand at room temperature for 24 hours

Concentration (ng/mL)			
	0 hour	24 hours	% change
Specimen 1	160.61	218.36	+36.0
Specimen 2	119.44	197.83	+65.6
Specimen 3	321.75	599.11	+86.2
Specimen 4	285.03	459.80	+61.3

2. Meconium emulsified in MECTEST solvent and kept at room temperature for 72 hours showed an increase in the concentration of morphine for the reason given above.

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

Concentration (ng/mL)			
	0 hour	72 hours	% change
Specimen 1	160.61	585.93	+264.8
Specimen 2	119.44	299.07	+150.4
Specimen 3	321.75	1200.57	+273.1
Specimen 4	285.03	1145.79	+302.0

3. The effect of freezing on the concentration of morphine in meconium is shown in the table below. At -15° C, morphine is relatively stable in meconium for at least 9 months.

Sample	Interval between test (days)	Opiate (ng/mL)	
		Original conc	Conc after freezing
1	322	1225	1217
2	322	1242	1100
3	322	156	252
4	170	144	113
5	170	823	545
6	170	2368	2149
7	170	0	0
8	109	0	0
9	120	4479	2996
10	109	0	0
11	109	0	0
12	109	0	0
13	109	0	0

V. Clinical Study:

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

Analysis of 50 meconium samples for opiate* by RIA and GC/MS

Sample	RIA (ng/mL)	GC/MS	Sample	RIA (ng/mL)	GC/MS
1	1217	+	26	2379	+
2	1100	+	27	2561	+
3	252	+	28	0	-
4	113	+	29	35	+
5	545	+	30	1838	+
6	2149	+	31	0	-
7	0	-	32	3517	+
8	0	-	33	747	+
9	2996	+	34	4507	+
10	0	-	35	2252	+
11	0	-	36	779	+
12	0	-	37	360	+
13	1507	+	38	958	+
14	1195	+	39	1946	+
15	0	-	40	1231	+
16	829	+	41	3074	+
17	217	+	42	1026	+
18	2379	+	43	0	-
19	137	+	44	1390	+
20	581	+	45	608	+
21	1646	+	46	233	+
22	118	+	47	0	-
23	156	+	48	822	+
24	0	-	49	2367	+
25	1881	+	50	0	-

* Morphine was the most common opiate identified by GC/MS; however, in some samples (#3, 4, 25, 29 and 33), the opiate was codeine. Since RIA detects opiate as a group, GC/MS is necessary to identify the specific opiate.

VI. Effect of Carryover

Patient samples may occasionally have very high concentrations of opiate. 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 medications containing morphine, codeine or other opioids.
2. Maternal ingestion of food or drinks containing poppy products.
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 micropipet, 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 carry-over 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)

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

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

And the 20, 50 and 80 percent "intercepts," where 20% = morphine 3-glucuronide concentration at 20 Percent Bound, etc.

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 which showed that a high concentration of the drugs which the pregnant animal was exposed to, were present in the meconium of their fetuses. [2-5] Drugs which 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 methodologic 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.

REFERENCES

1. Ostrea EM, Parks P, Brady M. Rapid isolation and detection of drugs in meconium of infants of drug dependent mothers. Clin Chem 1988; 34:2372-2373.

2. Ostrea EM, Brady MJ, Parks PM, Asensio DC, Naluz A. Drug screening of meconium in infants of drug dependent mothers. An alternative to urine testing. J Pediatr 1989; 115:474-477.

3. Ostrea EM, Lynn SN, Wayne RFL, Stryker JC. Tissue distribution of morphine in the newborns of addicted monkeys and humans. Dev Pharmacol Ther 1980; 1:163-170.

4. Lucena J, Silvestre MA, Raymundo AL, Ostrea EM. The effect of timing, dosage and duration of cocaine intake during pregnancy on the amount of cocaine in meconium in a rat model. Pediatr Res 1991; 29:62A.

5. Silvestre MA, Lucena J, Ostrea EM. The effect of timing, dosage and duration of morphine intake during pregnancy on the amount of morphine in meconium in a rat model. Pediatr Res 1991; 29:66A.

6. Ostrea EM, Brady MJ, Gause S, Raymundo AL, Stevens M. Drugs screening of newborns by meconium analysis: A large scale, prospective, epidemiologic study. Pediatrics 1992; 89:107-113.

7. Ostrea EM, Martier S, Welch R, Brady MJ. Sensitivity of meconium drug screen in detecting intrauterine drug exposure of infants. Pediatr Res 1990; 27:219A.

8. Callahan CK, Grant TK, Phipps P, Clark G et al. Measurement of gestational cocaine exposure: Sensitivity of newborn hair, meconium and urine. J Pediatr 1992; 120:763-8.

9. Maynard EC, Amuroso LP, Oh W. Meconium drug testing. Amer J Dis Child 1991; 145:650-652.

10. Ostrea EM, Romero A. Adaptation of the meconium test for mass drug screening. J Pediatr 1993; 122:152-154.

11. Ostrea EM, Romero A. Selection criteria for routine drug screening of infants by meconium analysis. Pediatr Res 1992; 31:215A.

12. Ostrea EM, Lizardo E, Tanafranca M. The prevalence of illicit drug exposure in infants in the NICU as determined by meconium drug analysis. Pediatr Res 1992; 31:215A.

13. Ostrea EM, Knapp DK, Romero A, Montes M, Ostrea AR. Meconium analysis to assess fetal exposure to active and passive maternal smoking. J Pediatr 1194; 124: 471-476.

14. Bandstra ES, Steele BW, Chitwood DD, et al. Detection of in utero cocaine exposure: A comparative methodologic study. Pediatr Res 1992; 31:58A

15. Ostrea EM, Knapp DK, Ostrea AR, Tannenbaum L, Salari V. A prospective study comparing systematic interview and analysis of maternal hair and meconium to determine illicit drug use during pregnancy. Pediatr Res 1994; 35:245A.

16. Montes M, Romero A, Ostrea EM, Ostrea AR. Improved method of GC/MS analysis of meconium for opiate, cocaine and cannabinoid. Pediatr Res 1993; 33:66A.

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