Antiretroviral Drugs in Meconium: Detection for Different Gestational Periods of Exposure

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Objectives To determine whether antiretroviral (ARV) medications can be detected in meconium from second or third trimester, labor and delivery (L&D), or postnatal exposures.

Study design Twenty ARV medications were quantified by liquid chromatography-tandem mass spectrometry in 598 meconium samples from uninfected infants born to pregnant women with HIV enrolled in the Pediatric HIV/AIDS Cohort Study.

Results ARV detection in meconium following third trimester exposure was 85.7%-94.4% for all ARVs except stavudine (0%, n = 2), likely because of low doses and a high limit for quantification. Of 107 samples with some second trimester only ARV exposures, meconium was positive for only lopinavir, tenofovir, or efavirenz in 11.8%-14.3% of exposed neonates; administration of these ARVs occurred between gestational weeks 25-28 in the positive samples. Days without lopinavir or tenofovir before delivery significantly correlated with decreasing concentrations of lopinavir and tenofovir in meconium. Tenofovir and lamivudine concentrations significantly correlated with increasing gestational age among infants with continuous second and third trimester exposure. Zidovudine given during L&D or for neonatal prophylaxis was detected in 95.1% and 94.6% of meconium samples, respectively.

Conclusions Changes in ARV treatments during pregnancy offered a unique opportunity to investigate ARV detection in meconium. ARVs in meconium primarily reflect third trimester ARV exposures, although 6 of 107 second trimester only exposures were detected. Zidovudine administration during L&D was detected in meconium indicating potential urine contamination or rapid incorporation into meconium. These data will improve interpretation of meconium drug test results. *(J Pediatr 2015;167:305-11)*.

Meconium begins to form in utero during the 12th gestational week and accumulates thereafter.[1,2] It is the specimen of choice for assessing fetal drug exposure,[3-11] offering advantages over neonatal urine with easier collection from diapers and a longer window for detection, primarily reflecting third trimester fetal drug exposures.[7,11]

Drug disposition in meconium is poorly understood and determining the time frame during gestation when drug exposure can be detected in meconium (the window of drug detection), is difficult. Most meconium forms in the final weeks before delivery,[12] when fetal growth, and fetal/placental blood and nutrient transport increase exponentially.[13,14] There is minimal information about meconium detection of second trimester fetal drug exposure. Our group previously evaluated opiate and cocaine meconium detection windows with 3 times-weekly urine collections to assess drug exposure timing.[7,11] We identified when drug relapse occurred, and concluded meconium reliably detected only third trimester drug use.[7,11]

Interpretation of drug concentrations in meconium also may be complicated by drug administration during labor and delivery (L&D). In 10 women who received 50-200 mg meperidine during labor, meconium was positive for

3TC	Lamivudine	M8	NFV hydroxy-tert-butylamide
ABC	Abacavir	NFV	Nelfinavir
ARV	Antiretroviral	NVP	Nevirapine
ATV	Atazanavir	PHACS	Pediatric HIV/AIDS Cohort Study
AZT	Zidovudine	RAL	Raltegravir
d4T	Stavudine	RTV	Ritonavir
DRV	Darunavir	SMARTT	Surveillance Monitoring for ARV Toxicities
EFV	Efavirenz		
FTC	Emtricitabine	SQV	Saquinavir
L&D	Labor and delivery	TDF	TFV disoproxil fumarate
LOQ	Limit of quantification	TFV	Tenofovir
LPV	Lopinavir		

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meperidine in all infants, and 3 infants also were positive for normeperidine.[15] These results may be explained by contamination of meconium with neonatal urine, rapid drug incorporation into meconium close to birth, or decreased P-glycoprotein expression late in pregnancy.[16] Zidovudine (AZT) is often administered during L&D of mothers with HIV and to infants exposed to HIV postnatally.[17] Utilizing maternal and neonatal AZT medication chart information provided a unique opportunity to investigate drug incorporation into meconium during L&D.

We evaluated windows of drug detection in meconium and determined whether meconium could detect antiretrovirals (ARVs) that were stopped or started during the second or third trimester. We also evaluated detection and quantification of AZT in meconium following maternal administration during L&D and/or infant postnatal administration.

Methods

The Surveillance Monitoring for ARV Toxicities (SMARTT) study of the Pediatric HIV/AIDS Cohort Study (PHACS) enrolled children exposed to HIV but not infected and their mothers infected with HIV who were prescribed ARVs during pregnancy to investigate long-term prenatal exposure effects of ARV.[18] Mothers and infants enrolled in SMARTT's Dynamic cohort between 22 weeks gestation and 1 week after birth. Institutional Review Boards at each site and the Harvard T.H. Chan School of Public Health approved the protocol, with maternal written informed consent.

Meconium was collected at 1 or more time-points within 72 hours of birth; multiple diaper collections were combined until transitional stool. Prior to 2011, meconium was refrigerated at study sites, and all specimens were frozen ($\leq -20°C$) until analysis (0-6 years). Beginning in 2011, meconium was frozen immediately after collection. Our novel liquid chromatography tandem mass spectrometry method quantified 20 ARV markers in 0.25 g meconium with limits of quantification (LOQs) from 10-500 ng/g.[19] Sixteen parent ARVs (abacavir [ABC]; amprenavir; atazanavir [ATV]; darunavir [DRV]; efavirenz [EFV]; emtricitabine [FTC]; lamivudine [3TC]; lopinavir [LPV]; nelfinavir [NFV]; nevirapine [NVP]; raltegravir [RAL]; ritonavir [RTV]; saquinavir [SQV]; stavudine [d4T]; tenofovir [TFV]; AZT) and four metabolites (ABC-carboxylate; ABC-glucuronide; NFV hydroxy-tert-butylamide [M8]; AZT-glucuronide) were measured, representing >99% of SMARTT ARV exposures.[20]

During validation, stability of ARV in meconium was investigated to determine if initial storage temperatures adversely affected quantification of ARV in meconium; all quantitative analytes were >82% stable under refrigerated (72 hours 4°C) and frozen (triplicate $-20°C$ freeze/thaw cycles) conditions.[19] Meconium concentrations of ARVs in samples collected before 2011 (n = 240) were compared with those collected in 2011 or later (n = 358) by a Mann-Whitney test to further evaluate stability.

Statistical Analyses

ARV prescription between 15 and 28 gestational weeks defined second trimester exposure and >28 weeks through delivery defined third trimester exposure. Among infants whose mothers were prescribed third trimester ARVs, group differences between samples with and without missed third trimester detection in meconium were evaluated with Mann-Whitney tests.

For ARVs with multiple second trimester-only detections, the association between days off the ARV predelivery and meconium concentration was investigated. Analysis included women with only second trimester use and those with any third trimester use. First, square-root, natural log, and $\log_{10}$ transformations were evaluated to normalize meconium ARV concentrations. A linear regression model was built for normalized meconium concentrations and maternal days off ARV. Exposure duration (days) was added a priori. Potential confounders (maternal tobacco, alcohol, or illicit drug use during pregnancy) were added to the model individually and retained when the effect estimate for the association between days off the ARV and meconium concentration changed $\geq$15%.

Associations between gestational age and ARV concentrations in meconium were investigated using linear regression for infants whose mothers were maintained continuously on the same ARV (entire second and third trimesters, with $\leq$3 days off drug). Sufficient data (n = 21-213) were available for 6 ARVs: TFV, FTC, 3TC, LPV, RAL, and RTV. For meconium TFV, maternal TFV disoproxil fumarate (TDF), a widely used TFV prodrug, was considered. RTV is commonly prescribed with other protease inhibitors as a pharmacokinetic boosting agent; when RTV was the sole protease inhibitor in a mother's regimen, samples were excluded from this analysis (n = 4). Potential confounders (maternal HIV RNA copies/mL before L&D, and maternal tobacco, alcohol, or illicit drug use during pregnancy) were evaluated separately and retained in the adjusted model when the effect estimate for the association between gestational age and meconium concentration changed $\geq$15%.

To investigate meconium detection of AZT with L&D and infant prophylaxis, 7 exposure categories were considered: (1) maternal third trimester, L&D, and neonatal prophylaxis; (2) only third trimester and L&D; (3) only L&D and neonatal prophylaxis; (4) only maternal third trimester and neonatal prophylaxis; (5) only L&D; (6) only neonatal prophylaxis; and (7) only third trimester. Meconium AZT detection prevalence and concentrations are reported and Kruskal-Wallis χ^2 tests assessed median concentration differences of AZT and AZT-glucuronide between groups. Significant associations were described by $P < .05$.

Results

Meconium ARV Detection in Third Trimester

Of 1750 SMARTT dynamic cohort infants enrolled through October 1, 2013, ARVs were quantified in 598 meconium

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