Poster #843

Abacavir Safety and Pharmacokinetics in Normal and Low Birth Weight Infants with HIV

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BACKGROUND

- Abacavir (ABC) is licensed for infants >3 months of age at a dose of 8 mg/kg twice daily
- WHO recommends ABC use in children with HIV ≥4 weeks of age and ≥3 kg using weight band dosing (starting at doses of up to 20 mg/kg)
- A recent safety report from the UK and Ireland of ABC prescribed at 2 to 8 mg/kg/dose in routine care in infants <3 months of age had no safety concerns1
- As ABC is metabolized in the liver, physiologic immaturity of enzyme pathways in young infants should have a major impact on ABC pharmacokinetics
- Women with HIV are at higher risk of delivering low birth weight (LBW,<2500g) and premature (<37 weeks gestation) infants
- No PK data for ABC are available in neonates or LBW infants, where differences in PK may be further potentiated

OBJECTIVE

- To describe ABC safety and pharmacokinetic data in normal birth weight (NBW) (≥2500-≤ 4000 gm) & LBW infants with HIV initiating ABC in the first 3 months of life

METHODS

Study Design

- IMPAACT P1106 is phase IV prospective, opportunistic, multi-arm pharmacokinetic and safety study of South African LBW and NBW infants with HIV < 3 months of age on selected ARVs and anti-TB medicines used for prophylaxis and/or treatment [NCT02383849]
- Recruitment in two IMPAACT sites in South Africa: Family Centre for Research with Ubuntu (FAMCRU) in Cape Town and the Perinatal HIV Research Unit (PHRU) in Johannesburg
- We present the results from LBW and NBW infants with HIV < 3 months of age initiating ARV treatment with 2NRTIs + lopinavir/ritonavir (LPV/r) by clinicians caring for these infants
- Infant characteristics & safety data were collected at study entry (within 7 days prior to LPV/r initiation) & at days 3-5, days 7-9 and week 2, 6, 10, 16 and 24 post LPV/r initiation
- Local Ethics Committees approved the study

Safety Reporting

- Adverse events (AEs), potentially harmful to NBW and LBW infants (< 3 months old) were classified as follows:
  - Expected: events pre-identified as commonly associated with prematurity or LBW
  - Unexpected: unanticipated events not commonly associated with prematurity
- AEs were evaluated from entry to week 24 and the primary composite safety endpoint included death and Grade 3/4 AEs

Sparse PK Blood Sampling

- Plasma samples for ABC drug level measurement were collected at:
  - Study Weeks 2, 10 and 24: pre-dose (C_0), 1.5- and 4-hours post-dose
  - Study Weeks 6 and 16: C_0 samples

Measurement of Drug Concentrations and PK Analysis

- ABC plasma levels were determined using a validated HPLC assay (LLOQ: 0.024 mg/L)
- Population means and variances of ABC PK parameters were estimated using non-linear mixed effects regression models (NONMEM Version VII)
- Infant characteristics (weight, sex, age, chronological or postnatal age (PNA), post-menstrual age (PMA) (PMA=gestational age + PNA) were evaluated for their inclusion in the model. The validity of the final model was evaluated using a visual predictive check

RESULTS

- 26 participants were enrolled between November 2015 and 6 April 2018
- 25 infants (18 LBW) on ABC + lamivudine + LPV/r were analyzed
- All infants received nevirapine prior to LPV/r initiation. Other medications included zidovudine n=14 (56%), trimethoprim-sulfamethoxazole n=24 (96%) and isoniazid n=2 (8%)

Table 1: Characteristics of Infants with HIV on ABC (n=25)

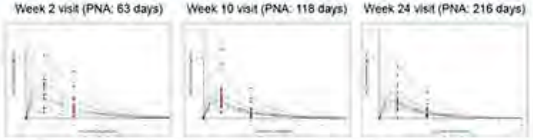
Characteristic	Median (range)
Gestational age at birth	36 (27 to 39) weeks
Birth weight	2250 (1360 to 3320) gm
Low birth weight (<2500 gm), N(%)	18 (72)
Postnatal age at study entry	6 (1.5 -11) weeks
Abacavir dose	10 (6-13) mg/kg/BID

Values are median and IQR unless specified otherwise Mixed race in 3 infants

Abacavir Population PK Model

- ABC concentrations were available for 24 (195 observations) infants with median (range) birth weight 2190 g (1360-3260) and median gestational age 36 weeks (32-37)
- ABC plasma levels were described by a 1-compartment model
  - Absorption rate constant (Ka) was 2.07.39 hr^{-1}; fixed to published value2
  - Body weight was allometrically scaled on both CL/F and Vd/F with exponents fixed to 0.75 and 1.0, respectively, and centred on a 5.4 kg infant
  - Maturation models including were assessed and inclusion of PMA on ABC oral clearance (CL/F) using a linear model was retained in the model. ABC CL/F increased by 2% per PMA week
- ABC population PK values: CL/F - 3.03 L/h/5.4 kg ; Vd/F - 11.0 L/5.4 kg

Figure 1: Individual Model Predicted ABC Concentration vs. Time Curves at PK Study Visits



- ABC plasma concentrations at predose, 1.5 and 4 hours post-dose

Figure 1: Mean (±SE) Individual Predicted ABC Concentration vs. Time Curves per PK Sampling Visit

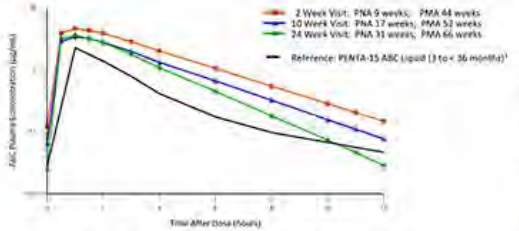


Table 2: Median infant characteristics and ABC PK parameters per PK visit

Study Visit	ABC Dose (mg/kg)	Weight (kg)	Postnatal age (weeks)	Postmenstrual age (weeks)	CL/F (L/hr/kg)	*$AUC0_{-12}$ (mg.hr/L)
Week 2 (n=16)	11 (6-13)	3.6 (2.4-5.4)	9 (6-13)	44 (38-50)	0.67 (0.24-1.42)	16.9 (4.6-48.7)
Week 10 (n=20)	9 (6-12)	5.2 (3.8-6.8)	17 (13-21)	52 (46-58)	0.79 (0.28-1.56)	10.7 (6.9-30.6)
Week 24 (n=20)	10 (7-12)	6.8 (5.1-8.9)	31 (27-35)	66 (59-71)	1.03 (0.34-1.97)	9.8 (4.4-33.9)

Historical ABC PK data in children: (i) PENTA-15: 3 to < 36 months AUC_{0-12}: 7.8 mg.hr/L[3] (ii) ARROW Trial: 3 to 6 years old (tablets): AUC_{0-12}: 7.8 mg.hr/L[4]

Safety

- Of the 25 infants with HIV in the safety analysis, 15 (60%) met the composite safety endpoint defined as death or Grade 3/4 AES
- One infant (birth weight 3320g) died of unknown cause at 8 weeks of life within 3 days of study entry. No PK samples collected
- 14 (56%) infants had Grade 3/4 Aes: gastroenteritis (n=4) & respiratory infection (n=4) most common
- Of the 14 infants with Grade 3/4 AEs:
  - 3 (12%) had Grade 3/4 Expected or Unexpected AEs
  - 2 (8%) had Grade 3/4 Expected AEs; and
  - 9 (36%) had Grade 3/4 Unexpected AEs

Table 3. Expected Adverse Events

Grade	Episodes (n=8)
3	Gastro-intestinal dysfunction (n=1); Respiratory insufficiency (n=1); Sepsis (n=2); Thrombocytopenia (n=1)
4	Sepsis (n=1); Hypotension (n=1); Electrolyte disorder (n=1)

Table 4. Unexpected Adverse Events

Grade	Episodes(n=29)
3	Gastrointestinal dysfunction (n=6); Respiratory tract infections (n=8); Bacterial sepsis (n=1); Underweight and malnutrition (n=3); Renal abnormality (n=2), Meningitis pneumococcal (n=1); Abnormal potassium (n=5)
4	Gastroenteritis (n=1); Abnormal potassium (n=2)

- **All Grade 3/4 Expected and Unexpected AEs were considered unrelated to ABC**
- All Grade 3/4 Expected AES resolved at a later visit, except for 1 infant who had Grade 2 sepsis at the last study visit
- All Grade 3/4 Unexpected AES improved, except for malnutrition (n=1), underweight (n=1) and a respiratory infection (n=1) present in 3 infants at the last study visit
- One Grade 2 aminotransferase (ALT) event was possibly related to antiretroviral therapy. The infant had a history of hepatotoxic traditional medicine ingestion. Resolution occurred following 2 weeks off all antiretrovirals, which were resumed without further complications
- No ABC hypersensitivity was reported

CONCLUSION/DISCUSSION

- ABC dosed 8 mg/kg twice daily was well tolerated in NBW and LBW infants initiated at <3 months of age through 9 months of age
- ABC exposures were higher during the first 3 months of life than older children (on liquid formulation) at the licensed doses but rapidly decreased as infants matured
- ABC exposures decreased rapidly as infants matured between 2 to 8 months of life
- ABC could be included in ART for young infants

REFERENCES

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