Clinical Infectious Diseases

BRIEF REPORT

Single Dose Abacavir Pharmacokinetics and Safety in Neonates Exposed to Human Immunodeficiency Virus (HIV)

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Abacavir is a potential option for prophylaxis and early treatment of human immunodeficiency virus (HIV), but no data are available in neonates. Ten neonates administered a single abacavir dose of 8 mg/kg before 15 days of life had substantially higher exposures than those reported in infants and children, with no reported adverse events.

Keywords. HIV; neonates; abacavir; pharmacokinetics.

Birth diagnosis and rapid initiation of combination antiretroviral treatment (cART) is increasingly recommended for treatment of neonates (<28 days of age) living with human immunodeficiency virus (HIV) [1]. The same cART initiated from birth in neonates at high risk of vertical HIV acquisition will simultaneously provide prevention and treatment for those neonates subsequently confirmed to be living with HIV [2]. However, initiating a triple antiretroviral drug regimen in neonates is challenging because of limited therapeutic options and the need for frequent dosing changes.

Only 5 antiretrovirals have sufficient data on dosing and safety for term (≥38 weeks gestational age) neonates exposed to HIV. Zidovudine, lamivudine, nevirapine, and raltegravir can be used from birth and lopinavir/ritonavir from 2 weeks of age [2]. The World Health Organization (WHO) recommends abacavir (ABC) in first-line cART for infants weighing at least 3 kg and from 4 weeks of age [1], but it is only licensed for infants older than 3 months. There are limited pharmacokinetics and safety data for infants <3 months of age with no neonatal ABC dosing guidance.

Abacavir is well absorbed orally and metabolized in the liver via alcohol dehydrogenase (ADH) and uridine diphosphate glucuronyltransferase (UGT) [3]. Rapid development and maturation changes in the first months of life makes predicting neonatal ABC drug exposures in neonates difficult. Current South African guidelines recommend infants living with HIV on cART to transition from zidovudine to ABC at 1 month of age [4], but it may be preferable to initiate ABC earlier to minimize the number of antiretroviral changes.

As pharmacokinetic data are lacking to guide clinicians on ABC use in neonates, whether for antiretroviral prophylaxis or treatment, we report on the pharmacokinetics and safety of single-dose ABC in neonates.

METHODS

Study Design

We performed an open-label single-dose pharmacokinetics and safety study of ABC in neonates exposed to HIV and infants <3 months of age living with HIV. In this report we present data from the cohort of neonates exposed to HIV. The study was conducted at Tygerberg Hospital, Cape Town, South Africa, and approved by the ethics committee of Stellenbosch University (N17/08/074). Mothers gave written informed consent.

Study Procedures

The study was composed of a single pharmacokinetic study visit with telephonic follow-up. Healthy, term infants receiving zidovudine and nevirapine for prevention of vertical HIV transmission with a negative birth HIV nucleic acid test were eligible. The routine prevention of mother-to-child transmission service at the hospital referred potential study participants to the study team for consideration. Neonates received a single dose of 8 mg/kg of ABC liquid. Blood for quantification of ABC plasma concentrations were taken at 1, 2, 4, 6, and 8 hours post-ABC dose. There were no feeding restrictions. All mothers were to be contacted 1 month after the ABC dosing to check for adverse events. All HIV nucleic acid test results were extracted from the National Health Laboratory Service database.

Pharmacokinetic Analysis

Samples were stored at −70°C and shipped to the AMS-PHPT Clinical Pharmacology laboratory at Chiang Mai University, Thailand, for analysis. Plasma ABC concentrations were quantified using a validated liquid chromatography-triple quadrupole mass spectrometry assay over the range of 0.02 to 2.5 μg/mL.

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This laboratory participates in the DAIDS/NIH funded Clinical Pharmacology Quality Assurance Program. ABC pharmacokinetic parameters were computed using a noncompartmental analysis (Phoenix64, V8.2, Certara, Princeton, NJ, USA). Calculated parameters included: area under the plasma drug concentration-time curve (AUC), maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), apparent oral clearance (CL/F), and last concentration measured postdose (C_{last}). Nonpharmacokinetic statistical analyses were performed using Stata software (v11.0, StataCorp, College Station, TX, USA).

RESULTS

Study Population

Ten term neonates (8 female) were enrolled. The median (range) gestational age at birth was 39 (38–42) weeks, and the median (range) birth weight was 3158 (2540–4150) grams. All mothers were treated with tenofovir, emtricitabine, and efavirenz. Eight infants exposed to HIV received daily nevirapine monotherapy, and 2 received daily nevirapine and twice daily zidovudine.

Abacavir Pharmacokinetics

On the pharmacokinetic sampling day, the median postnatal age was 10 (6–15) days, and the median weight was 3320 (2850–4440) grams. A median ABC dose of 8.1 mg/kg (8.0–8.4) mg/kg was administered at the same time as each infant's antiretroviral prophylaxis. The individual characteristics of the neonates and their ABC pharmacokinetic parameters are described in Table 1. The median (range) C_{max} of ABC was 4.4 (2.9–7.2) μg/mL, T_{max} was 2.0 (1.0–4.0) hours, and C_{last} (or C_8) was 1.9 (1.2–2.6) μg/mL. The median AUC_{0-8} and AUC_{0-inf} were 26.3 (15.5–35.7) and 39.1 (22.3–50.9) μg.hr/mL, respectively, with apparent median oral clearance (CL/F) value of 3.5 (2.6–6.3) mL/min/kg.

Table 1. Individual Characteristics and Abacavir Pharmacokinetic Parameters

Subject	GA (wks)	Birth Wt (g)	C_{max} (μg/mL)	AUC_{0-8h} (μg.hr/mL)	$AUC_{0-\infty}$ (μg.hr/mL)	Half-life (hr)	CL/F (mL/min/kg)
1	40	3035	4.42	24.49	29.62	2.47	4.57
2	38	3310	4.39	23.40	33.09	4.09	4.04
3	38	4150	7.19	35.31	47.21	3.63	2.86
4	38	2540	2.91	15.49	22.34	4.12	6.28
5	38	2885	4.21	25.24	46.46	6.35	3.00
6	42	3300	6.79	35.70	45.98	3.23	2.91
7	40	3330	6.00	27.27	34.33	3.13	3.94
8	39	3190	4.09	22.12	30.92	4.02	4.40
9	39	3125	5.05	30.41	43.91	3.85	3.06
10	38	2960	4.16	28.24	50.89	5.99	2.63
Median	39	3158	4.41	26.26	39.12	3.93	3.50
Min	38	2540	2.91	15.49	22.34	2.47	2.63
Max	42	4150	7.19	35.70	50.89	6.35	6.28

Abbreviations: AUC, area under the plasma concentration vs time curve; CL/F, apparent oral clearance; C_{max}, maximum plasma concentration; GA, gestational age; Max, maximum; Min, minimum; Wt, weight.

Safety

No adverse events were observed on the pharmacokinetic sampling day. One month following the pharmacokinetic sampling visit, 9 of the 10 mothers could be contacted, and all reported healthy infants. No skin rash, fever, or vomiting was observed in the 2 weeks following single-dose ABC. All 9 infants had a repeat negative HIV nucleic acid test between 10 and 16 weeks of life. One mother could not be reached by telephone; however, this infant had a negative HIV nucleic acid test registered on the NHLS database by 19 weeks of age.

DISCUSSION

This is the first study to our knowledge describing the pharmacokinetic and safety of a single-dose of ABC in term neonates receiving the licensed dose for children ≥3 months of age. ABC exposure observed were higher than those reported in infants and children, likely due to slower drug clearance through immature enzyme pathways in this population. Despite high exposure, ABC was well tolerated with no reported adverse events.

ABC can be given once or twice daily with an AUC proportional to the dose [3]. At the approved adult dose of 300 mg twice daily, the mean AUC_{0-12} is 6.02 μg.hr/mL [3]. Approximately double the adult ABC dose is required for children (due to higher clearance) to achieve comparable adult exposure [3]. A study in children receiving weight-band dosing with a fixed-dose ABC tablet (~12.5 mg/kg twice daily) had ABC AUC_{0-12} in the range of 11.3–17.3 μg.hr/mL [5]. In our study, the median AUC exposure following a single dose of 8 mg/kg were 2- to 3-fold higher. Interestingly, a recent population pharmacokinetic analysis of ABC in severely malnourished children with HIV who were dosed using World Health Organization (WHO) weight band dosing, also found an increased ABC exposure in the range of 12.2–36.4 μg.hr/mL among those with treatment success [6].

Clearance is typically low in neonates undergoing rapid developmental and physiological changes in the first months of life. ABC CL/F is reported to be a function of postmenstrual age, evident from recently presented data from the IMPAACT P1106 trial where ABC CL/F increased from 11.2 to 17.2 mL/min/kg between 2 and 9 months of life in normal and low-birth weight infants with HIV [7]. As expected, the ABC CL/F in our study (performed in neonates before 15 days of life) was even lower (2.6–6.3 mL/min/kg). A preliminary report from a congress in 2000 reported a similar ABC CL/F range of 1.7–3.0 mL/min/kg in 9 neonates after a single 2 mg/kg dose [8]. Differences in the timing of the pharmacokinetic sampling between studies could explain the minor difference observed, but the age of the neonates at the time of pharmacokinetic assessment were not reported in the earlier study. Taken together, these data show a substantially lower ABC CL/F in neonates compared to infants and young children.

Despite higher exposure and reduced clearance observed in our study, no ABC associated adverse events were identified. The risk for ABC hypersensitivity is <1 % for all children [9]. Recent findings from 2 large observational cohorts further support ABC's favorable safety profile. Of 139 European infants with HIV initiating ABC aged < 3 months (20 neonates), only 19 (14%) discontinued the drug by 12 months, 4 due to a possible ABC adverse event occurring within 7 days of starting ABC (1 metabolic acidosis, 1 diarrhea, and 2 possible hypersensitivity reactions were reported) [10]. Of 931 South African infants with HIV initiating ABC aged <3 months (96 neonates), only 61/798 (8%) discontinued ABC permanently; 1 hypersensitivity reaction was reported in an infant on day 73 of life [11].

There are several limitations to our study. First, due to delays in the availability of birth HIV nucleic acid test results, earlier pharmacokinetic sampling could not be performed. Second, ABC was only administered at a single dose, and assessing a variety of doses would have been preferable. Finally, no laboratory assessments following the single dose were made to evaluate possible drug-related toxicity.

A shift from the current infant antiretroviral prophylaxis approaches to a simplified framework harmonized with early treatment was endorsed at the WHO convened PADO-4 meeting [12]. Administration of ABC from birth, instead of zidovudine, would be more aligned with current treatment guidelines for those neonates with confirmed HIV (ie, minimizing drug changes) and also provide an alternative option to the few antiretrovirals available. The high exposure and reduced clearance in our study show that reduced liquid ABC doses in neonates are required if comparable infant exposures at licensed doses are targeted, and this should be further explored through the application of population pharmacokinetic modeling. However, there remains an urgent need to further study solid formulations of ABC in neonates, including the feasibility of using generic fixed-dosed antiretroviral combinations (FDC), which often require administration of higher than approved doses but have greatly simplified and accelerated access to cART for infants and children globally.

Notes

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References

1. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection 2016. Recommendations for a public health approach. Available at: http://www.who.int/hiv/pub/arv/arv-2016/en/. Accessed 4 May 2020.
2. Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Available at: https://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf. Accessed 4 May 2020.
3. Abacavir package insert 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020977s024,020978s028lbl.pdf. Accessed 4 May 2020.
4. Western Cape Health Department. The Western Cape consolidated guidelines for HIV treatment: prevention of mother-to-child transmission of HIV (PMTCT), children, adolescents and adults (amended version) 2020. Available at: https://www.westerncape.gov.za/assets/departments/health/hiv_guidelines_16012020.pdf. Accessed 4 May 2020.
5. Kasirye P, Kendall L, Adkison KK, et al; ARROW Trial Team. Pharmacokinetics of antiretroviral drug varies with formulation in the target population of children with HIV-1. Clin Pharmacol Ther **2012**; 91:272–80.
6. Archary M, Mclleron H, Bobat R, et al. Population pharmacokinetics of abacavir and lamivudine in severely malnourished human immunodeficiency virus-infected children in relation to treatment outcomes. Br J Clin Pharmacol **2019**; 85:2066–75.
7. Cressey T, Bekker A, Cababasay M, et al. Abacavir safety and pharmacokinetics in normal and low birth weight infants with HIV [abstract no. 843]. 27th Conference on Retroviruses and Opportunistic Infections; 8–11 March 2020; Boston, MA, USA, CROI Foundation partners with the International Antiviral Society-USA (IAS -USA), **2020**. Available at: https://www.croiconference.org/abstract/abacavir-safety-and-pharmacokinetics-in-normal-and-low-birth-weight-infants-with-hiv/
8. Johnson GM, Rodman JH, McDowell J. Preliminary analysis of abacavir succinate (ABC) pharmacokinetics in neonates differs from adults and young children [abstract no. 720]. 7th Conference on Retroviruses and Opportunistic Infections. 30 January 2000–2 February 2000. San Francisco, CA, USA, **2000**.
9. Jesson J, Dahourou DL, Renaud F, Penazzato M, Leroy V. Adverse events associated with abacavir use in HIV-infected children and adolescents: a systematic review and meta-analysis. Lancet HIV **2016**; 3:e64–75.
10. Crichton S, Collins IJ, Turkova A, et al. Abacavir dosing, effectiveness, and safety in young ingants living with HIV in Europe [abstract no. 844]. 27th Conference on Retroviruses and Opportunistic Infections. 8–11 March 2020; Boston, MA, USA, **2020**. Available at: https://www.croiconference.org/abstract/abacavir-dosing-effectiveness-and-safety-in-young-infants-living-with-hiv-in-europe/
11. De Waal R, Rabie H, Technau K, et al. Abacavir safety and efficacy in young infants in South African observational cohorts [abstract no. 845]. 27th Conference on Retroviruses and Opportunistic Infections. 8–11 March 2020. Boston, MA, USA, **2020**.
12. Penazzato M, Townsend CL, Rakhmanina N, et al; PADO4 participants. Prioritising the most needed paediatric antiretroviral formulations: the PADO4 list. Lancet HIV **2019**; 6:e623–31.