Effect of Sorbitol on Lamivudine Pharmacokinetics Following Administration of EPIVIR® Solution in Adults

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Kimberly Adkison,[1] Cynthia McCoig,[2] Allen Wolstenholme,[3] Yu Lou,[4] Zhiping Zhang,[4] Amy Eld,[3] Katy Hayward,[5] Mark Shaefer[1]

[1]ViiV Healthcare, Research Triangle Park, NC, USA; [2]ViiV Healthcare, Tres Cantos, Spain; [3]GlaxoSmithKline, Collegeville, PA, USA; [4]PAREXEL International, Durham, NC, USA; [5]ViiV Healthcare, Brentford, Middlesex, UK

Introduction

- The ARROW pediatric trial (randomization 3) demonstrated that once-daily lamivudine (3TC) and abacavir (ABC) was noninferior to twice-daily dosing in terms of HIV virologic suppression in 2- to 12-year-old African children
  - A subgroup analysis by drug formulation showed that, irrespective of dosing frequency, pediatric subjects receiving solutions had lower rates of virologic suppression and developed viral resistance more frequently than those receiving tablet formulations. Therefore, the EPIVIR® product label was changed to recommend tablets as the preferred formulation for pediatric patients[1]
- An ARROW pharmacokinetic (PK) substudy conducted in 2- to 4-year-old children on 3TC/ABC/zidovudine (ZDV) showed that the relative bioavailability of 3TC solution was 37% lower than that of 3TC in a tablet formulation.[2] Two IMPAACT studies also showed lower 3TC solution bioavailability in children 0.5 to 12 years old
  - P1056 showed that exposure of 3TC solution given in combination with stavudine and nevirapine (NVP) liquid formulations was 29% lower than 3TC in a triple-combination tablet[3]
  - P1069 showed that exposure of 3TC solution given in combination with ZDV and NVP liquid formulations was 44% lower than 3TC exposure from a triple-combination tablet[4]
- In contrast to the pediatric results, a prior relative bioavailability study in adults demonstrated that 3TC tablets and capsules provided equivalent exposures to 3TC solution when both the test and reference formulations were administered alone
- Sorbitol, a nonabsorbed sugar alcohol and commonly used sweetener for liquid medications, has been implicated in several drug interactions
  - Sorbitol increases osmotic pressure in the intestine, resulting in accelerated small intestinal transit time and decreased absorption/bioavailability of some drugs (eg, ranitidine, cimetidine)[5,6]
- Unlike the adult relative bioavailability studies, children in ARROW, P1056, and P1069 were receiving 3TC in combination with one or more antiretroviral and antibiotic liquid formulations known to contain sorbitol, including ABC (ZIAGEN®; ViiV Healthcare, Research Triangle Park, NC), NVP (VIRAMUNE®; Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT), and cotrimoxazole
- It was hypothesized that the lower concentrations of 3TC solution observed in the pediatric studies could have resulted from an interaction between 3TC and the sorbitol found in co-administered medications[7]
- The objective of the present study was to determine if there is an absorption-based drug interaction between sorbitol and 3TC

Methods

- This study (NCT02634073) was a single-center, open-label, treatment-randomized (Williams design), 4-way crossover in 16 subjects randomized to receive a single dose of each of the 4 treatments shown in Table 1

Table 1. Treatment Doses

Treatment[a]	Dose and Rationale
A 3TC alone	EPIVIR 300 mg; adult once-daily dose
B 3TC + low-dose sorbitol	EPIVIR 300 mg + sorbitol 3.2 g; to mimic sorbitol amount in an adult dose of VIRAMUNE (NVP) suspension
C 3TC + medium-dose sorbitol	EPIVIR 300 mg + sorbitol 10.2 g; to mimic sorbitol amount in an adult dose of ZIAGEN (ABC) solution
D 3TC + high-dose sorbitol	EPIVIR 300 mg + sorbitol 13.4 g; to mimic combined sorbitol amount in adult doses of ZIAGEN and VIRAMUNE

[a]3TC 300 mg was administered as 30 mL of 10 mg/mL EPIVIR Oral Solution (ViiV Healthcare, Research Triangle Park, NC). Sorbitol was administered as 3.6, 11.3, or 14.9 mL of a sorbitol aqueous solution 70% w/w USP (Geritrex, Mount Vernon, NY).

- All doses were administered with 240 mL of water after an overnight fast. There was a ≥7-day between-dose washout period
- Serial plasma PK samples were collected for 48 hours post-dose, and 3TC concentrations were measured by liquid chromatography-tandem mass spectrometry. Standard safety assessments were made throughout the study
- 3TC plasma PK parameters were calculated by noncompartmental methods. Analysis of variance, considering treatment as fixed effect and subject as random effect, was performed using SAS Mixed Linear Models procedure to compare plasma 3TC log-transformed PK parameters. The ratio of geometric least squares means (test vs reference) and 90% confidence intervals (CIs) were estimated

Results

Subject Disposition

- 37 subjects were screened; 16 were randomized and completed the study
- Mean age was 40.6 years and mean weight was 78.1 kg. 14/16 subjects were male. 10 subjects were White, and 6 were African American/African

Safety

- A total of 3 subjects (19%) had 5 adverse events (gastroenteritis, vessel puncture–site pain, myalgia, dizziness, vaginal infection), with vaginal infection considered to be drug related. There were no serious AEs, Grade 3/4 AEs, vital sign abnormalities, or laboratory abnormalities reported as AEs

Pharmacokinetics

- Mean 3TC plasma concentration-time profiles are shown in Figure 1
- Selected plasma 3TC PK parameters are provided in Table 2, and a summary of the statistical treatment comparisons is provided in Table 3

Figure 1. Mean (± SD) Plasma Concentration-Time Profile of 3TC Following Administration of EPIVIR® Solution Alone or With Various Doses of Sorbitol Solution

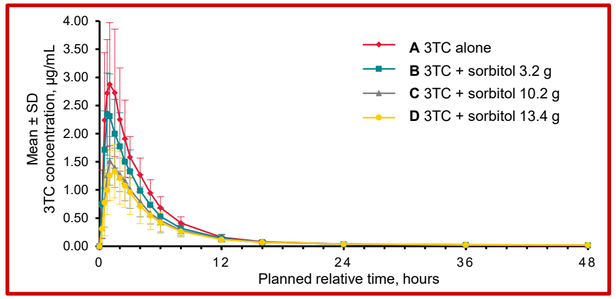

Table 2. Summary of Geometric Mean (CVb%) Plasma 3TC Pharmacokinetic Parameters

Treatment	N	C_{max}, µg/mL	T_{max}, h[a]	$AUC_{(0-24)}$, µg·h/mL	$AUC_{(0-\infty)}$, µg·h/mL
A 3TC alone	16	3.34 (34.9)	0.75 (0.50-1.50)	12.4 (23.6)	13.2 (22.3)
B 3TC + 3.2 g sorbitol	16	2.42 (32.7)	1.00 (0.50-1.50)	9.96 (22.6)	11.3[b] (21.2)
C 3TC + 10.2 g sorbitol	16	1.60 (27.2)	1.00 (0.50-2.50)	7.54 (23.7)	8.93 (22.1)
D 3TC + 13.4 g sorbitol	16	1.52 (30.9)	1.26 (0.50-3.00)	6.91 (28.9)	8.60[c] (24.1)

C_{max}, maximum observed concentration; T_{max}, time of C_{max}; $AUC_{(0-24)}$, area under concentration-time curve from time zero to 24 hours; $AUC_{(0-\infty)}$, AUC from time 0 extrapolated to infinity. [a]median (range). [b]n=14. [c]n=13.

Table 3. Summary of 3TC Treatment Comparisons

	Ratio of Geometric Least Squares Means (90% CI)		
PK Parameter	**B vs A[a] N=16**	**C vs A[a] N=16**	**D vs A[a] N=16**
$AUC_{(0-24)}$	0.803 (0.747, 0.864)	0.608 (0.566, 0.655)	0.557 (0.518, 0.599)
$AUC_{(0-\infty)}$	0.855[b] (0.799, 0.914)	0.677 (0.635, 0.721)	0.637[c] (0.594, 0.682)
C_{max}	0.724 (0.657, 0.798)	0.479 (0.434, 0.527)	0.454 (0.412, 0.500)

C_{max}, maximum observed concentration; T_{max}, time of C_{max}; $AUC_{(0-24)}$, area under concentration-time curve from time zero to 24 hours; $AUC_{(0-\infty)}$, AUC from time 0 extrapolated to infinity. [a]Treatment A: 3TC alone; treatment B: 3TC + sorbitol 3.2 g; treatment C: 3TC + sorbitol 10.2 g; treatment D: 3TC + sorbitol 13.4 g. [b]n=14. [c]n=13.

Discussion

- 3TC was readily absorbed (lag time=0) following all treatment regimens
- Median T_{max} occurred between 0.75 and 1.26 hours post-dose, with later T_{max} associated with sorbitol co-administration
- Sorbitol co-administration resulted in a dose-dependent reduction in 3TC plasma exposures, with higher doses of sorbitol (3.2 g, 10.2 g, and 13.4 g, respectively) resulting in lower 3TC exposures
  - C_{max} decreased by 28%, 52%, and 55%
  - $AUC_{(0-24)}$ decreased by 20%, 39%, and 44%
  - $AUC_{(0-\infty)}$ decreased by 14%, 32%, and 36%
- Sorbitol had the greatest effect on C_{max} and $AUC_{(0-24)}$, suggesting that sorbitol's effect was primarily on absorption and bioavailability of 3TC
- These adult study results provide the likely mechanism for the lower 3TC solution exposures observed in the aforementioned pediatric studies in which the 3TC solution was dosed concomitantly with other liquid medications containing sorbitol (eg, ABC, NVP, cotrimoxazole)
- The dose-dependent effects of sorbitol and differences between adults and children in gastrointestinal physiology, intestinal volume, and cumulative dose and frequency of sorbitol administration make it difficult to precisely extrapolate the magnitude of interaction observed in adults to children

Conclusions

- Sorbitol has a dose-dependent effect on 3TC PK and is the likely mechanism for the lower 3TC solution exposures in pediatric studies
- To manage this drug interaction, chronic co-administration of sorbitol-containing medicines and 3TC should be avoided
- Specifically, with regard to children, 3TC given concomitantly with sorbitol-containing medicines should be used to treat HIV only when an all-tablet regimen cannot be used and the benefits of treatment outweigh possible risks, including lower virologic suppression

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