Cerebrospinal Fluid Abacavir Concentrations in HIV-positive Patients Following Once-daily Administration

Cerebrospinal Fluid Abacavir Concentrations in HIV-positive Patients Following Once-daily Administration

A Calcagno [1], C Pinnetti[2], A De Nicolò [1], E Scarvaglieri[1], M Gisslen[3], M Tempestilli[2], A D'Avolio A[1], V Fedele[2], G Di Perri[1], A Antinori [2], S Bonora[1].

1. Unit of Infectious Diseases, Department of Medical Sciences, University of Torino, Torino, Italy, 2. Clinical Department, National Institute for Infectious Diseases "Lazzaro Spallanzani," Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Rome, Italy; 3. Department of Infectious Diseases, The Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

Running title: Once-daily abacavir CSF penetration

Key words: central nervous system; pharmacokinetics; age; cerebrospinal fluid; abacavir; protease inhibitors.

Word count: 1220 (abstract 74)

Tables: 1

Figures: 1

Corresponding author: Andrea Calcagno
Ospedale Amedeo di Savoia, ASL TO2
C.so Svizzera 164
10149, Torino, Italy
+390114393884
andrea.calcagno@unito.it

Competing Interest: The authors declare no competing interest.

Funding: The study was supported by internal funding.

Abstract

Abacavir is a widely used nucleotide reverse transcriptase inhibitor whose cerebrospinal fluid (CSF) exposure has been previously assessed in twice-daily recipients. We studied abacavir CSF concentrations in 61 and 9 HIV-positive once-daily and twice-daily abacavir intakers. Patients on once-daily abacavir had higher plasma and CSF concentrations (96 vs. 22 ng/mL, p=0.038 and 123 vs. 49 ng/mL, p=0.038) but similar CSF-to-plasma ratios (0.8 vs. 0.5, p=0.500). CSF abacavir concentrations were adequate in once-daily receiving patients.

Introduction

Abacavir (ABC) is a largely used once-daily HIV nucleoside reverse transcriptase inhibitor included in first-line regimens by international guidelines.(1) Even though the clinical relevance is debated, higher penetration of antiretrovirals into the cerebrospinal fluid (CSF) has been associated with a lower concentrations of CSF HIV RNA and, in some studies, with better cognitive function.(2)(3) The concentration penetration/effectiveness score (CPE) ranks ABC as 3 (out of 4) and therefore the compound has been included within the medium-high score stratus. However most of the data were generated with the 300 mg twice-daily dose: its CSF to plasma ratio (CPRs) was reported to be 36% (28-46) although with significant variability.(4) The aim of this study was to compare CSF concentrations (and CPRs) in patients administered once versus twice-daily ABC.

Methods

ABC-administered patients undergoing lumbar punctures for clinical reasons or included in longitudinal studies were included in Turin (Ospedale Amedeo di Savoia, ASL “Città di Torino”) and Rome (Istituto Nazionale per le Malattie Infettive “Lazzaro Spallanzani”); signed informed consent was given by all subjects and ethics approval was obtained by each Institution (Comitato Etico Interaziandale di Orbassano, n. 103/2015). Plasma and CSF samples were concomitantly obtained (less than 30 minutes apart). ABC concentrations were measured at steady state in the same externally validated laboratory (University of Torino) through a validated HPLC/MS-MS method (with a limit of detection of 4.88 ng/mL).(5) Trough concentrations were those withdrawn

21-27 (once-daily) and 10-14 (twice-daily) hours after drug intake.

CSF to serum albumin ratio (CSAR, calculated as CSF albumin (mg/L)/serum albumin (g/L)), was used to evaluate BBB function. BBB damage definition was derived from age-adjusted Reibergrams (normal if below 6.5 in patients aged <40 years and below 8 in patients >40 years).(6)

Data are expressed as medians (interquartile range) and compared through non-parametric tests (Spearman's test for linear correlation and Mann-Whitney or Kruskal-Wallis for when a categoric variable was compared with a linear one). All concentrations were used for identifying predictors of CSF penetration while only trough values were used for comparing once and twice-daily administration. Coefficients of variation (CV) are calculated as the ratio between the standard deviation and the mean.

Key ligands in this article are hyperlinked to corresponding entries in PubChem, the Open Chemistry Database, available at https://pubchem.ncbi.nlm.nih.gov.

Results

70 patients (85.7% male, 95% Caucasians) were included; age (years) and BMI (kg/m^2) were 50.2 (46.2-58.7) and 23.4 (20.9-25.6), respectively In 60 patients chronic hepatitis status was known: 21 (35%) per HCV+, 3 (5%) were HBV+ and 6 (10%) had a previous diagnosis of liver cirrhosis. Fourty four subjects (62.8%) were asymptomatic and received LPs for non Hodgkin's lymphoma staging (33, 47.1%,) or in the context of longitudinal studies (11, 15.7%); among the remaining 26 patients HIV-encephalopathy (8, 11.4%), HIV-associated neurocognitive impairment (6, 8.6%), CNS opportunistic infections (6, 8.6%) and various neurological presentations (6 including two cases of seizures of new onset). Baseline features are listed in Table 1.

Most frequent co-administered drugs were PIs (67.1 %) followed by NNRTIs (28.6%), NRTIs-only (5.7%) and INSTIs (5.7%). CD4+ T lymphocyte cell count was 302/uL (137-462). After excluding patients with plasma HIV RNA >1000 copies/mL (n=3), 62 subjects had available plasma and CSF HIV RNA: they were below 50 copies/mL in 47 (74.6%) and 43 (68.3%) subjects. CSF escape (defined as detectable HIV RNA in CSF while undetectable in plasma or CSF HIV RNA ≥ 1 Log_{10}

higher than plasma level) was observed in 13 individuals (20.6%); no association was observed between ABC levels, detectability or schedule of administration and the prevalence of CSF escape.

Samples were withdrawn over the range interval but after a median of 12 hours (12-20) after drug intake; 18 were trough samples. Median ABC plasma and CSF concentrations were 58 ng/mL (<1-815, CV=140%) and 106 ng/mL (21-304, CV=149%). ABC CPRs ranged from 0 to 4.92 [median 0.80, IQR (0.17-1.87), CV=99%]. Among those with undetectable plasma concentrations (17, 25%), 9 were non-detectable in the CSF while 8 showed low but detectable CSF concentrations [35 ng/mL (11-67)]. A direct correlation was observed between ABC plasma concentrations and time from drug intake (rho= 0.406, p=0.005); this was not observed for CSF concentrations (rho=0.212, p=0.148) and CPRs (rho=-0.092, p=582).

The drug was administered once-daily in 61 (87.1%) patients; CSF ABC concentrations over time are shown in figure 1 (stratified by frequency of intake). The two groups' baseline characteristics were comparable with the exception of non-significantly higher CD4 cell count (332 vs. 155/uL, p=0.062) in the once-daily group. Patients on once-daily ABC had higher plasma and CSF concentrations (96 vs. 22 ng/mL, p=0.038 and 123 vs. 49 ng/mL, p=0.038) but CPRs were similar (0.8 vs. 0.5, p=0.500). Trough values showed the same trend: higher plasma concentrations (1377 vs. <4.88 ng/mL, p=0.02) but similar CSF values (152 vs. 24 ng/mL, p=0.08) and CPRs (0.2 vs. 0, p=0.08). In once-daily recipients CSF ABC concentrations were associated with ABC plasma levels (rho=0.865, p<0.001) and, weakly, with age (rho=0.275, p=0.046): patients receiving PIs had higher CSF [220 (64-529) vs. 70 (17-134) ng/mL, p=0.013] and plasma [500 (35-1531) vs. 42 (<4.88-100) ng/mL, p=0.002] concentrations. HCV+ once-daily recipients showed higher CPR as compared to HCV- subjects [1.57 (0.80-2.35) vs. 0.36 (0.12-1.28), p=0.007].

CSAR were available in 28 patients: median value was 5.35 (4.12-6.87) with 4 individuals (14.3%) presenting an altered blood brain barrier permeability. No linear correlation was observed between CSAR and ABC CSF concentrations or CSF to plasma ratios (as well as no effect of an impaired BBB was noted).

No difference was observed in ABC CSF to plasma ratios according to neurological confounding conditions and or CSF HIV-1 escape (Kruskal-Wallis and Mann-Whitney tests p values > 0.05).

Discussion

In this small study we observed that patients on once-daily abacavir had CSF ABC concentrations and CSF to plasma ratios higher than previously reported (in median 80%). Our control group of twice-daily recipients was small (n=9) but showed higher CPRs than what reported by Capparelli (36%) and Antinori (4%).(7) This may be explained by the significant interpatient variability, by the concomitant use of PIs (not reported in the previous studies) and potentially by the older age of our patients. Protease inhibitors may influence drug penetration by inhibiting drug efflux transporters such as p-glycoprotein and breast cancer resistant protein as shown in vitro by Marzolini et al.(8) Age may be a contributing factor in increasing drug concentration in the CSF: increased blood brain barrier permeability, lower CSF production and reduced transporters' function have been suggested in older adults.(9)(10) The only available, but yet unpublished, study reported a steep increase in CSF tenofovir and efavirenz concentration with increasing age.(11) Additionally a high prevalence of CSF escape was observed and this may have influenced our results (in terms of confounding conditions or pharmacokinetic features following ongoing inflammation). Nevertheless when abacavir (coadministered with lamivudine and dolutegravir) was administered to naïve patients an excellent efficacy in the CSF (both 2 and 16 weeks after treatment initiation) confirming the drug compartmental efficacy when used in combination with other active compounds.(12)

Limitations of current analysis include the small sample size, the inclusion of single time points and non-trough concentrations. ABC CSF concentrations and CPRs were however more stable over the time interval as compared to plasma levels and as previously reported by Cusini et al.(13)

In conclusion in once-daily abacavir treated HIV-positive patients, high CSF ABC and CSF to plasma ratios were observed suggesting the current CPE ranking may be appropriate even with the commonly used once a day schedule.

What is already known about this subject

Abacavir is an efficacious HIV reverse transcriptase inhibitor; it is considered to be active in the central nervous system although most of the knowledge on the drug compartmental

pharmacokinetics was obtained in patients administered twice daily.

What this study adds.

Once daily administered abacavir is associated with cerebrospinal fluid concentrations and CSF to plasma ratios similar to what was observed in participants receiving the drug twice a day. Given the large use of this compound in single tablet regimens, this data support its neuropenetration/neuroefficacy profile.

Acknowledgements

This study was presented at the 9th Italian conference on AIDS and Antiviral Research, Siena, 2017.

Tables

	Once Daily	**Twice Daily**
	n or median (% or IQR)	
n:	61	9
Age: years	51 (46.4-58.1)	49.3 (43.7-60.1)
Male gender: n (%)	51 (83.6%)	9 (100%)
BMI: Kg/m^2	23.4 (20.9-25.6)	25.2 (21.4-25.6)
CD4: Cells/uL	332 (137-524)	155 (130-275)
CD4 nadir: Cells/uL	132 (60-288)	94 (16-543)
plasma HIV RNA: Log_{10} copies/mL	1.59 (<1.27-1.75)	1.65 (<1.27-2.17)
CSF HIV RNA: Log_{10} copies/mL	1.59 (1.59-2)	1.59 (<1.27-2.03)
CSF cells: n/mm^3	1 (0-3)	2 (1-6)
CSF proteins: mg/dL	42 (33-56)	39 (25-96)
CSAR	5.1 (4.0-6.0)	7 (6.8-7.6)
Time after abacavir intake: hours	13 (11.5-24)	12 (11.5-12.5)
ARV classes: NNRTI	20 (32.7%)	0
NRTIs only	2 (3.3%)	2 (22.2%)
PI	35 (57.4%)	7 (77.8%)
INSTI	4 (11.4%)	0
Indication for LP: Asymptomatic	7 (11.5%)	4 (44.4%)
HAND	6 (9.8%)	0
Neurological symptoms	4 (6.6%)	2 (22.2%)
HIV encephalopathy	7 (11.5%)	1 (11.1%)
CNS-opportunistic infections	6 (9.8%)	0
NHL	31 (50.8%)	2 (22.2%)

Table 1. Baseline characteristics of the included patients stratified according to once-daily or

twice-daily abacavir intake. “IQR”, interquartile range; “BMI”, body mass index; “CSF”, cerebrospinal fluid; “CSAR”, CSF to serum albumin ratio; “ARV”, antiretroviral; “NNRTI”, non nucleoside reverse transcriptase inhibitors; “NRTI”, nucleos(t)ide reverse transcriptase inhibitors; “PI”; protease inhibitor; “INSTI”, integrase strand transfer inhibitor; “LP”, lumbar puncture; HAND”, HIV-associated neurocognitive disorders; “CNS”, central nervous system; “NHL”, non Hodgkin’s lymphomas (screening for meningeal involvement).

Figure Legends

Figure 1. Abacavir cerebrospinal fluid to plasma ratios according to time after dose and stratified for once or twice-daily schedule.

References

1. DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents [Internet]. 2016 [cited 2016 Nov 30]. Available from: http://aidsinfo.nih.gov/guidelines
2. Hammond ER, Crum RM, Treisman GJ, Mehta SH, Marra CM, Clifford DB, et al. The cerebrospinal fluid HIV risk score for assessing central nervous system activity in persons with HIV. Am J Epidemiol. 2014 Aug 1;180(3):297–307.
3. Vassallo M, Durant J, Biscay V, Lebrun-Frenay C, Dunais B, Laffon M, et al. Can high central nervous system penetrating antiretroviral regimens protect against the onset of HIV-associated neurocognitive disorders? AIDS Lond Engl. 2014 Feb 20;28(4):493–501.
4. Capparelli EV, Letendre SL, Ellis RJ, Patel P, Holland D, McCutchan JA. Population pharmacokinetics of abacavir in plasma and cerebrospinal fluid. Antimicrob Agents Chemother. 2005 Jun;49(6):2504–6.
5. UPLC-MS/MS Method for the Simultaneous Quantification of Three New Antiretroviral Drugs, Dolutegravir, Elvitegravir and Rilpivirine, and Other Thirteen Antiretroviral Agents Plus Cobicistat and Ritonavir Boosters in Human Plasma [Internet]. PubMed Journals. [cited 2017 Jun 19]. Available from: https://ncbi.nlm.nih.gov/labs/articles/28219799/
6. Reiber H. External quality assessment in clinical neurochemistry: survey of analysis for cerebrospinal fluid (CSF) proteins based on CSF/serum quotients. Clin Chem. 1995 Feb;41(2):256–63.
7. Antinori A, Perno CF, Giancola ML, Forbici F, Ippolito G, Hoetelmans RM, et al. Efficacy of cerebrospinal fluid (CSF)-penetrating antiretroviral drugs against HIV in the neurological compartment: different patterns of phenotypic resistance in CSF and plasma. Clin Infect Dis Off Publ Infect Dis Soc Am. 2005 Dec 15;41(12):1787–93.
8. Marzolini C, Mueller R, Li-Blatter X, Battegay M, Seelig A. The brain entry of HIV-1 protease inhibitors is facilitated when used in combination. Mol Pharm. 2013 Jun 3;10(6):2340–9.
9. Nau R, Sörgel F, Eiffert H. Penetration of Drugs through the Blood-Cerebrospinal Fluid/Blood-Brain Barrier for Treatment of Central Nervous System Infections. Clin Microbiol Rev. 2010 Oct;23(4):858–83.
10. Toornvliet R, van Berckel BNM, Luurtsema G, Lubberink M, Geldof AA, Bosch TM, et al.

Effect of age on functional P-glycoprotein in the blood-brain barrier measured by use of (R)-[(11)C]verapamil and positron emission tomography. Clin Pharmacol Ther. 2006 Jun;79(6):540–8.
11. Croteau D, Letendre S, Best B, Clifford D, Gelman B, Marra C, McArthur J, McCutchan JA, Simpson D, Grant I. Older age is associated with higher ARV concentrations in CSF in HIV + individuals. In Seattle, WA, USA; 2012.
12. Letendre SL, Mills AM, Tashima KT, Thomas DA, Min SS, Chen S, et al. ING116070: a study of the pharmacokinetics and antiviral activity of dolutegravir in cerebrospinal fluid in HIV-1-infected, antiretroviral therapy-naive subjects. Clin Infect Dis Off Publ Infect Dis Soc Am. 2014 Oct;59(7):1032–7.
13. Cusini A, Vernazza PL, Yerly S, Decosterd LA, Ledergerber B, Fux CA, et al. Higher CNS penetration-effectiveness of long-term combination antiretroviral therapy is associated with better HIV-1 viral suppression in cerebrospinal fluid. J Acquir Immune Defic Syndr 1999. 2013 Jan 1;62(1):28–35.