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Abstract

Herein, the authors report the case of a patient diagnosed with hepatitis C virus who was treated with sofosbuvir-velpatasvir (400/100 mg). As the patient was unable to swallow whole tablets, therapeutic drug monitoring was performed to evaluate the effect of crushing sofosbuvir-velpatasvir tablets on drug absorption and global exposure.

Keywords: Sofosbuvir, velpatasvir, crushing, pharmacokinetics, exposure

CLINICIAN

The patient was a 70-year-old woman with a history of rectal cancer in 2009 and a right oropharyngectomy owing to carcinoma in 2016. She had been a heavy smoker with excessive alcohol intake for several years. A CT-scan performed in February 2019 as part of the oropharyngeal carcinoma follow-up revealed 2 liver tumors (20 mm each) in the right lobe of the liver. Liver enzymes were moderately increased: aspartate aminotransferase (AST) = 87 IU/L (N < 31); alanine aminotransferase (ALT) = 67 IU/L (N < 34); γ-glutamyltransferase (GGT) = 152 IU/L (N < 38). Albumin (42 g/L), total bilirubin (6 µmol/L), and prothrombin index were normal. Alpha-fetoprotein was dramatically increased up to 14,207 g/L (N < 10), and the biopsy of the tumor and non-tumorous liver confirmed the diagnosis of bifocal hepatocellular carcinoma (HCC) developed on a non-cirrhotic METAVIR F3 fibrotic liver.[1] Hepatitis B and human immunodeficiency virus serology were negative. Hepatitis C virus (HCV) serology was positive, and active replication was confirmed by HCV RNA detection with a high viral load of 6.8 log IU/mL and genotype 1b virus infection. She underwent satisfactory surgical resection of the HCC tumors in May 2019.

The multidisciplinary team evaluating the HCV cases in the institution proposed a treatment with a direct-acting antiviral (DAA) agent comprising glecaprevir and pibrentasvir (Maviret, AbbVie) [2] for 8 weeks. This combination was selected for its high efficacy and short treatment duration. However, owing to previous oropharyngectomy, the patient was not able to swallow tablets.

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Glecaprevir–pibrentasvir is a fixed-dose combination tablet indicated in the treatment of HCV with a pangenotypic activity at the dosage of 300/120 mg per day (3 tablets of 100/40 mg simultaneously). The drug is a combination of a NS5A (a protein responsible for regulation of the viral replicative complex and involved in assembly and release of viral particles) inhibitor (pibrentasvir) and a NS3/4A protease inhibitor (glecaprevir), which, as clearly stated in the summary of product characteristics (SmPC), should be taken with food and should not be chewed or crushed. The drug is formulated as a bilayer tablet; therefore, crushing can lead to unintended variations in bioavailability with a decrease in area under the curve (AUC) of 27–61% for glecaprevir and an increase in AUC of 21–83% for pibrentasvir compared to the exposure from whole tablets.[2,3] No other formulation such as an oral solution or dispersible tablet is available; therefore, the drug cannot be given to the patient.

However, no clear recommendation is available for sofosbuvir–velpatasvir (Epclusa), an RNA-dependent RNA polymerase NS5B and NS5A inhibitor with pangenotypic anti-HCV activity. Indeed, SmPC does not recommend crushing these tablets because of their bitter taste, but there is a lack of information about the effect of crushing on sofosbuvir–velpatasvir pharmacokinetics. Velpatasvir is also highly sensitive to the acidic stomach environment, as underlined by the decrease in drug exposure ranging from 26% to 60% when given with

omeprazole,[4–6] and influenced by food with an increase in AUC of 20% to 30% with a high and moderate fat meal, respectively.[7] Moreover, taking the drug with an acidic beverage may enhance velpatasvir absorption.[5] We then suggested administering crushed sofosbuvir–velpatasvir with an acidic beverage during a meal and conducting therapeutic drug monitoring (TDM) of sofosbuvir and velpatasvir by monitoring peak on the first day and global exposure of the drugs by measuring steady-state trough plasma drug concentrations (C_{ss}).

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Sofosbuvir–velpatasvir treatment for 12 weeks was approved by the multidisciplinary team, according to French and European guidelines for the management of patients with acute and chronic HCV infections.[8,9] In addition, TDM was planned to assess the absorption of the drugs. Blood samples were collected on the first day of treatment before DAA administration (trough concentration (C_{min}) and 2 (C2), 3 (C3), and 4 (C4) hours after the first DAA administration. Additional trough blood samples measured at steady-state (Css) were collected 1 week and 10 weeks after commencement of treatment.

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Sofosbuvir and velpatasvir peak (C_{max}) and Css are well documented, with sofosbuvir having a C_{max} of 511 ± 174 ng/mL [10] and a rapid elimination (half-life elimination: 30 min), leading to a trough concentration generally below the limit of quantification of the analytical method, and velpatasvir having C_{max} and Css of 575 ± 213 and 42 ± 28 ng/mL respectively.[7,11] Therefore, these parameters could be easily compared to the value measured in the patient. Drug levels were determined using a liquid chromatography-tandem

mass spectrometry method validated according to the European Medicines Agency guidelines.[12] C_{min}, C2, C3, and C4 for sofosbuvir were <20, 1,544, 1,497, and 642 ng/mL, respectively, while for velpatasvir, these were <20, 285, 966, and 1,244 ng/mL, respectively. C_{ss} at day 7 and week 10 were <20 ng/mL for sofosbuvir and 116 and 107 ng/mL for velpatasvir.

The time to reach maximal concentration (t_{max}) was 1 and 3 h for sofosbuvir and velpatasvir respectively.[7,11,13] The results of sofosbuvir and velpatasvir TDM were consistent with an increase in the absorption of both drugs in this patient after crushing the tablet. Sofosbuvir is rapidly metabolized, and its C_{ss} values were consistent with its pharmacokinetic parameters.[14] More importantly, velpatasvir C_{ss} values were in favor of a correct exposure to the drug (C_{ss} range 14–70 ng/mL; mean reported concentration ± standard deviation).[11]

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The drugs seemed to be very well resorbed. When compared with usual C_{max}, their concentrations were in favor of an increase in sofosbuvir and velpatasvir absorption when crushed. Velpatasvir C_{ss} measurements appeared to be related to a high drug exposure without any accumulation of the compound as confirmed by the very similar C_{ss} reported at week 1 and week 10. After completion of sofosbuvir–velpatasvir combination treatment, the patient reported no treatment-related adverse events. Liver parameters improved: AST, 13 IU/L; ALT, 30 IU/L; GGT, 20 IU/L; total bilirubin, 6 µmol/L; and albumin, 47 g/L. HCV viral load decreased rapidly, became undetectable after 4 weeks of treatment, and remained undetectable after 12 weeks of treatment.

In conclusion, this report describes the first case of a successful HCV treatment in a treatment-naïve patient by using crushed sofosbuvir–velpatasvir tablets. TDM showed that, when taken with food and an acidic beverage, the absorption of both drugs increased. As velpatasvir is a low solubility drug, particularly in gastric pH above 4.5, crushing the tablet may enhance the drug solubility. TDM of velpatasvir trough C_{ss} also allowed the verification of treatment exposure during the treatment period, thereby ensuring its efficacy.

Reference List

[1] Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. *Hepatology* 1996;24:289–293.

[2] European Medicines Agency. Maviret®Summary of product characteristics, https://www.ema.europa.eu/en/documents/product-information/maviret-epar-product-information_en.pdf (accessed August 8, 2019).

[3] Oberoi RK, Zhao W, Sidhu DS, et al. A phase 1 study to evaluate the effect of crushing, cutting into half, or grinding of glecaprevir/pibrentasvir tablets on exposures in healthy subjects. *J Pharm Sci.* 2018;107:1724–1730.

[4] Mogalian E, McNally J, Shen G, et al. Drug-drug interaction profile of sofosbuvir/velpatasvir fixed-dose combination. *J Hepatol.* 2016;64:S613–S614.

[5] van Seyen M, Colbers A, Abbink EJ, et al. Concomitant intake of Coca-Cola® to manage the drug-drug interaction between velpatasvir and omeprazole studied in

healthy volunteers. *Clin Pharmacol Ther*. Epub ahead of print July 17, 2019. DOI: 10.1002/cpt.1569.

[6] Smolders EJ, Jansen AME, ter Horst PGJ, et al. Viral hepatitis C therapy: Pharmacokinetic and pharmacodynamic considerations: A 2019 update. *Clin Pharmacokinet*. Epub ahead of print 21 May 2019. DOI: 10.1007/s40262-019-00774-0.

[7] European Medicines Agency. Epclusa® Summary of product characteristics, https://www.ema.europa.eu/en/documents/product-information/epclusa-epar-product-information_en.pdf (accessed 8 August 2019).

[8] European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2018. *J Hepatol* 2018;69:461–511.

[9] Association française pour l'étude du foie (AFEF). Recommendations on treatment of hepatitis C, https://afef.asso.fr/wp-content/uploads/2018/06/VF-INTERACTIF-RECO-VHC-AFEF-v2103.pdf (accessed October 24, 2019).

[10] European Medicines Agency. Sovaldi® Summary of product characteristics, https://www.ema.europa.eu/en/documents/variation-report/sovaldi-h-c-2798-ii-0036-epar-assessment-report-variation_en.pdf (accessed August 8, 2019).

[11] Mogalian E, German P, Kearney BP, et al. Preclinical pharmacokinetics and first-in-human pharmacokinetics, safety, and tolerability of velpatasvir, a pangenotypic hepatitis C virus NS5A inhibitor, in healthy subjects. *Antimicrob Agents Chemother.* 2017;61:e02084-16.

[12] European Medicines Agency. Guideline on bioanalytical method validation. 2011, https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-bioanalytical-method-validation_en.pdf (2011, accessed October 24, 2019).

[13] Brieva T, Rivero A, Rivero-Juarez A. Pharmacokinetic drug evaluation of velpatasvir plus sofosbuvir for the treatment of hepatitis C virus infection. *Expert Opin Drug Metab Toxicol.* 2017;13:483–490.

[14] German P, Mathias A, Brainard D, et al. Clinical pharmacokinetics and pharmacodynamics of ledipasvir/sofosbuvir, a fixed-dose combination tablet for the treatment of hepatitis C. *Clin Pharmacokinet.* 2016;55:1337–1351.