Pharmacokinetic similarity demonstrated after crushing of the elbasvir/grazoprevir fixed-dose combination tablet for HCV infection

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Background: Finding a suitable treatment for HCV patients with swallowing disorders is still a major challenge. In practice, direct-acting antivirals are crushed without knowledge of adequate absorption. Crushing can alter drug exposure, possibly leading to treatment failure, development of resistance or toxicity. Currently, there is no information about crushing of the fixed-dose combination tablet of elbasvir/grazoprevir; therefore, crushing of this tablet is not recommended.

Objectives: To investigate the influence of crushing on the pharmacokinetics of the elbasvir/grazoprevir fixed-dose combination tablet.

Methods: We conducted an open-label, two-period, randomized, cross-over, Phase I, single-dose trial in 11 healthy adult volunteers. Subjects randomly received whole-tablet elbasvir/grazoprevir or crushed and suspended elbasvir/grazoprevir in a fasted state. Pharmacokinetic similarity criteria (90% CIs lie within 70%–143% acceptance range) were used for AUC₀⁻<sub>∞</sub> and AUC₀⁻<sub>72</sub>.

Results: Mean plasma concentration–time curves of elbasvir and grazoprevir showed similar pharmacokinetic profiles. The primary pharmacokinetic parameters AUC<sub>₀⁻<sub>∞</sub></sub> and AUC<sub>₀⁻<sub>72</sub></sub> of elbasvir and grazoprevir after intake of a crushed tablet were on average 12%–16% higher compared with the whole tablet, but 90% CIs were all within the predefined boundaries of pharmacokinetic similarity. Crushing leads to a higher C<sub>max</sub> of grazoprevir (42%); no significant difference was found between treatments with regard to the C<sub>max</sub> of elbasvir. No serious adverse events were reported during the trial.

Conclusions: Pharmacokinetic similarity could be demonstrated for a crushed and suspended tablet compared with a whole tablet, without impacting drug safety or efficacy. Crushed and suspended administration of elbasvir/grazoprevir can be used in patients with swallowing disorders.

Introduction

Worldwide, approximately 71 million people are suffering from chronic HCV infection. Although asymptomatic in early stages, HCV is one of the main causes of chronic liver disease. If left untreated, chronic HCV may lead to liver-related morbidity, including decompensation, hepatocellular carcinoma and death. Chronic HCV has become a curable disease and direct-acting antivirals (DAAs) cure >90% of patients.¹

Optimal target exposure to DAAs is needed to achieve therapeutic success. Oral drug delivery can be challenging in patients with swallowing disorders. These patients have prolonged oesophageal drug-transit time, which affects pharmacokinetics and compromises effectiveness. Swallowing disorders are prevalent and it is estimated that 10%–40% of adults have difficulties swallowing solid oral medications.²⁻⁴ Most DAAs are formulated as fixed-dose combination tablets and are big in size. If not authorized in the drug label, manipulation of drugs, such as crushing, is
technically off-label. As a consequence, there is no therapy available for patients with swallowing disorders and efficacy after interruption or discontinuation of the expensive HCV therapy is unknown.

Although this is contraindicated, it is common practice to crush DAA tablets and dissolve or suspend the powder to ease administration, without information about efficacy and safety.\(^5\)-\(^7\) However, crushing tablets can lead to altered pharmacokinetics; either a decrease\(^8\) or an increase\(^9\) in exposure may occur. This may possibly lead to treatment failure, development of resistance or toxicity. A 2018 study by Oberoi et al.\(^7\) demonstrated that grinding or crushing of glecaprevir/pibrentasvir, a fixed-dose DAA tablet, had a serious impact on exposures in healthy subjects, leading to a prohibition (in the label text) to chew, crush or break the tablets.\(^10\)

Elbasvir/grazoprevir, a potent once-daily fixed-dose combination tablet, is approved for the treatment of HCV genotype 1a, 1b and 4 infection. It is a combination of the NS5A inhibitor elbasvir and the NS3/4A PI grazoprevir. The biopharmaceutical characteristics of the drug formulation make the 21x10 mm elbasvir/grazoprevir tablet without a specific release profile a suitable candidate for crushing.\(^3\)

In 2018, Yap et al.\(^11\) described successful treatment of a patient treated with elbasvir/grazoprevir for a 16 week course through a percutaneous endoscopic gastrostomy (PEG) tube. There are no further data available supporting the efficacy, safety and pharmacokinetics of crushed elbasvir/grazoprevir. The aim of this study was to investigate the influence of crushing on the pharmacokinetics of elbasvir/grazoprevir.

**Methods**

This open-label, two-period, randomized, cross-over, Phase I, single-dose trial in healthy adult volunteers was conducted in April 2019 at the Radboud University Medical Center, Nijmegen, The Netherlands.

The protocol was approved by the local ethics committee of Arnhem-Nijmegen and registered at ClinicalTrials.gov under number NCT03817619. Data were collected using Castor (Castor Electronic Data Capture CB, Amsterdam, The Netherlands).

Healthy volunteers who were eligible for inclusion had to be between 18 and 55 years of age, had to weigh at least 40 kg with a BMI of 18.5–35 kg/m², had to be able and willing to sign the Informed Consent Form, healthy volunteers who were eligible for inclusion had to be between 18 and 55 years of age, had to weigh at least 40 kg with a BMI of 18.5–35 kg/m², had to be able and willing to sign the Informed Consent Form, had to be in good age-appropriate health condition and had to not have smoked more than 10 cigarettes, 2 cigars or 2 pipes per day for at least 3 months prior to Day 1. Main exclusion criteria were: positive serology for hepatitis B or C; creatinine clearance below 60 mL/min/1.73 m²; sensitivity/idosyncrasy to the medicinal products or excipients used in this study; relevant history or current condition that might interfere with drug absorption, distribution, metabolism or excretion; pregnant or breastfeeding; therapy with any drug except for acetaminophen and/or a hormonal and non-hormonal intrauterine device; abuse of drugs or alcohol; and febrile illness within 3 days before Day 1.

The study was designed to show pharmacokinetic similarity between a whole elbasvir/grazoprevir tablet and a crushed tablet. Tablets were crushed in a plastic crushing bag with the Medline Silent Knight\(^10\) pill crusher following the ‘Procedures for Crushing Zepatier for NG or Stomach Tube Administration’.\(^12\) Subjects randomly received the following oral treatment regimen: reference treatment (whole single-dose elbasvir/grazoprevir tablet) or test treatment (crushed single-dose elbasvir/grazoprevir tablet) in a fasted state with 250 mL of water. To prevent any residual crushed tablet in the crushing bag or the dosing cup, both were twice rinsed with 15 mL of water. The suspension was stirred thoroughly until the crushed tablet appeared to be evenly dispersed in the water and no substantial clumps remained just before administration. A washout period of 14 days was scheduled between each treatment period.

The sample size for this study was calculated using a mixed linear model with fixed factors subject, period and treatment assuming an intra-subject variability for AUC of ~26% for grazoprevir and ~27% for elbasvir.\(^13\) A total sample size of nine evaluable subjects was considered sufficient for a power of 80% to evaluate absence of difference between whole and crushed tablet. A total of 11 subjects were included to account for possible dropouts.

Volunteers had to fast for at least 8 h prior to administration of elbasvir/grazoprevir on the pharmacokinetic sampling days. Water was allowed up to 1 h before and 1 h after administration of elbasvir/grazoprevir. For every healthy volunteer, a pharmacokinetic curve was collected up to 72 h after intake for determination of elbasvir and grazoprevir concentrations. Blood samples were collected in EDTA plasma tubes at the following timepoints: 0 h (pre-dose) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 48 and 72 h post-ingestion after observed intake of the study medication.

The main objective of this study was to investigate the influence of crushing on the pharmacokinetics of elbasvir/grazoprevir in healthy volunteers. The primary pharmacokinetic parameter of interest was the AUC extrapolated to infinite time (AUC\(_{0→∞}\)) and to 72 h (AUC\(_{0→72}\)). Secondary pharmacokinetic parameters were the maximum plasma concentration (C\(_{max}\)), time to C\(_{max}\) (T\(_{max}\)) and terminal half-life (t\(_{1/2}\)). The data obtained in this study were analysed according to the EMA ‘Guideline on the Investigation of Bioequivalence’ and FDA ‘Guidance for Industry: Statistical Approaches to Establishing Bioequivalence’.\(^14,\)\(^15\)

Concentrations of elbasvir and grazoprevir in plasma were analysed by the use of a validated LC-MS/MS method. The calibration range was 3.0–1500 μg/L for elbasvir and grazoprevir in plasma.\(^16,\)\(^17\) Pharmacokinetic parameters were determined by non-compartmental analysis in WinNonlin (version 8.1, Certara, Princeton, NJ, USA); AUCs were calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations (linear-up/log-down). Geometric mean ratios (GMRs) with 90% CIs of AUC\(_{0→∞}\), AUC\(_{0→72}\) and C\(_{max}\) were calculated for the crushed tablet versus the whole tablet after log transformation of within-subject ratios using the bioequivalence module (mixed model) in WinNonlin/Phoenix, with fixed effects treatment, period, sequence and subject within sequence. The AUC\(_{0→∞}\) and AUC\(_{0→72}\) were valid if it was possible to estimate a reliable T\(_{max}\) and the C\(_{max}\); covered more than 80% of the extrapolated part of the AUC. For a reliable estimate of T\(_{max}\), at least three samples are required during the terminal log-linear phase in combination with a coefficient of determination (R\(^2\)) of >0.8. The two treatments were considered pharmacokinetically similar if the 90% CIs of the GMRs of AUCs were within 70% to 143%. These no-effect boundaries are based on recommendations concerning elbasvir/grazoprevir use when co-administered with interacting drugs; the boundaries represent the acceptable change in systemic exposure that is considered not significant enough to warrant clinical action.\(^10\) Comparisons of T\(_{max}\) were performed using the Wilcoxon signed-rank test with SPSS software (Version 25). Statistical significance was set at P < 0.05.

Furthermore, safety and tolerability of a single-dose crushed elbasvir/grazoprevir tablet was evaluated based on adverse event (AE) monitoring and laboratory tests. AEs were graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table, version 2.1, July 2017).

**Results**

Eleven healthy adult volunteers (five male and six female; 100% white race) were enrolled in this study, all of whom completed the study. Median (range) age was 26 (22–54) years and median...
(range) BMI was 24.3 (18.1–27.1) kg/m². All subjects provided written informed consent for this study.

All 22 plasma concentration–time curves of elbasvir were valid. Seven of the 22 plasma concentration–time curves of grazoprevir (4 in the reference treatment and 3 in the test treatment) in four volunteers could not be included for AUC₀–₇₂ analysis because the majority of the data points were below the lower limit of qualification (LLOQ) (<3.0 µg/L) (Figure S1 and Table S1, available as Supplementary data at JAC Online). A marked inter-individual variability in plasma concentration–time curves of grazoprevir was observed, as shown by their high percentage coefficient of variation values of 144% for the whole tablet and 70% for crushed tablet for the Cₘₐₓ.

Pharmacokinetics

AUC

Figure 1 shows the mean plasma concentration–time curves of elbasvir and grazoprevir for the reference and test treatments. Table 1 shows the pharmacokinetic parameters for all compounds for each treatment. It also shows the GMRs of the crushed tablet versus the whole tablet and the corresponding 90% CIs. The AUC₀–₇₂ of elbasvir of the crushed tablet were both 12% higher compared with the whole tablet. The AUC₀–₇₂ and AUC₀–₇₇₂ of grazoprevir of the crushed tablet were also higher compared with the whole tablet (13% and 16%, respectively). Figure S2 demonstrates grazoprevir AUC₀–₇₂ of the individual participants. The 90% CIs of AUC₀–₇₂ and AUC₀–₇₇₂ for both compounds fell within the predefined boundaries of pharmacokinetic similarity of 70%–143%.

Cₘₐₓ

The Cₘₐₓ of elbasvir increased by 10% and the Cₘₐₓ of grazoprevir by 42% after intake of the crushed tablet compared with the whole tablet. Pharmacokinetic similarity between the crushed tablet and the whole tablet could not be demonstrated for grazoprevir as the 90% CIs for Cₘₐₓ of grazoprevir exceeded the required limits of 70%–143%. The 90% CIs of the Cₘₐₓ of elbasvir fell within the pharmacokinetic similarity limits of 70%–143%. Notably, no significant difference in the Tₘₐₓ of elbasvir between the treatment groups was evident (P = 0.67; Wilcoxon signed-rank test), but the Tₘₐₓ of grazoprevir was significantly shorter after intake of the crushed tablet compared with the whole tablet (P = 0.02; Wilcoxon signed-rank test).

AEs

No serious AEs were reported during the trial. Four healthy adult volunteers reported a total of five AEs. Of these, three were judged to be probably or possibly related to elbasvir/grazoprevir. One volunteer experienced transient asymptomatic elevations of ALT and AST defined as grade 2 (2.5 to <5.0 × upper limit of normal) after both administrations. There was one case of headache (grade 1). Haematoma and sinus pain were reported as unrelated (grade 1).

Discussion

In this study we showed that crushing of elbasvir/grazoprevir did not affect the main pharmacokinetic properties. Thus, pharmacokinetic similarity could be demonstrated.

Our data showed an increase in grazoprevir Cₘₐₓ and a significantly shorter Tₘₐₓ after crushing, without toxicity being observed. The mean grazoprevir Cₘₐₓ for a single crushed dose of 100 mg was 1.5-fold higher than the mean grazoprevir Cₘₐₓ for the whole tablet. In our opinion, the increased grazoprevir Cₘₐₓ observed in this study is not clinically relevant in terms of safety because the safety and tolerability of grazoprevir have been demonstrated for multiple doses up to 800 mg once daily (8-fold higher than the licensed dose of 100 mg) for 12 weeks in a Phase II study. In addition, exposure (AUC) rather than Cₘₐₓ has been related to an increased risk of late ALT elevations and AUC was not influenced by crushing in our study. However, individual considerations are
recommended for patients with a risk for high grazoprevir exposure, such as patients with cirrhosis or using interactive medication.10

Remarkably, in 2018, Oberoi et al.7 demonstrated that manipulation of glecaprevir/pibrentasvir tablets had a serious impact on exposure in healthy volunteers. Crushing the tablets resulted in a 36% lower AUC0–72 for glecaprevir and a 33% higher AUC0–72 for pibrentasvir. The exact reason for the different impact was not clear, but may be due to differences in disintegration and dissolution caused by the pH and the location of absorption.7 The aqueous solubility of grazoprevir and elbasvir is low, with highest solubility being under basic and acid conditions, respectively. Grazoprevir has high permeability and is classified as BSC class IV.19 Theoretically, crushed application and dissolution caused by the pH and the location of absorption. Therefore, it is unlikely that crushing is the cause of the low exposure. A plausible explanation is the high inter-individual variability as shown by their high percentage coefficient of variation values of 144% and 70% for the Cmax of grazoprevir. This is also described in Phase I studies.15,13,20 The LLOQ was established for a crushed and suspended tablet compared with a whole tablet. In our opinion, the results are reliable and valid because the power is sufficient to evaluate the grazoprevir plasma concentrations for all healthy volunteers following a single dose of 100 mg of grazoprevir administered under fasted conditions.13,20 In our opinion, the results are reliable and valid because the power is sufficient to evaluate the absence of difference in AUC with a total of nine evaluable subjects, so the missing data has no clinically relevant consequences for the conclusion.

In our practice, we are regularly asked by physicians how to treat HCV patients with swallowing difficulties or patients who require a feeding tube. In addition to our results, unpublished in vitro data of MSD showed at least 92% recovery of both components (elbasvir and grazoprevir) through three types of tube.

In conclusion, pharmacokinetic similarity could be demonstrated for a crushed and suspended tablet compared with a whole tablet, without impacting drug safety or efficiency of this generally well-tolerated drug. Crushed and suspended administration of elbasvir/grazoprevir can be used in patients with swallowing disorders or patients who require a feeding tube.
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Supplementary data
Figures S1 and S2 and Table S1 are available as Supplementary data at JAC Online.

References
1 European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2018. J Hepatol 2018; 69: 461–511.
2 Marquis J, Schneider MP, Payot V et al. Swallowing difficulties with oral drugs among polypharmacy patients attending community pharmacies. Int J Clin Pharm 2013; 35: 1130–6.
3 Schiele JT, Quinzler R, Klimm HD et al. Difficulties swallowing solid oral dosage forms in a general practice population: prevalence, causes, and relationship to dosage forms. Eur J Clin Pharmacol 2013; 69: 937–48.
4 Kappelle WF, Siersema PD, Bogte A et al. Challenges in oral drug delivery in patients with esophageal dysphagia. Expert Opin Drug Deliv 2016; 13: 645–58.
5 Jindracek L, Stark J. Treatment of chronic hepatitis C virus infection with crushed ledipasvir/sofosbuvir administered via a percutaneous endoscopic gastrostomy tube. J Pharm Pract 2018; 31: S24–4.
6 Lau ETL, Steadman KJ, Cichero JAY et al. Dosage form modification and oral drug delivery in older people. Adv Drug Deliv Rev 2018; 135: 75–84.
7 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: 1724–30.
8 Best BM, Capparelli EV, Diep H et al. Pharmacokinetics of lopinavir/ritonavir crushed versus whole tablets in children. J Acquir Immune Defic Syndr 2011; 58: 385–91.
9 Roskam-Kwint M, Bollen P, Colbers A et al. Crushing of dolutegravir fixed-dose combination tablets increases dolutegravir exposure. J Antimicrob Chemother 2018; 73: 2430–4.
10 EMA. Zepatier: Summary of Product Characteristics. 2016. https://www.ema.europa.eu/en/documents/product-information/zepatier-epar-product-information_en.pdf.
11 Yap JE, Jaiswal P, Ton L et al. Successful treatment of chronic hepatitis C infection with crushed elbasvir/grazoprevir administered via a percutaneous endoscopic gastrostomy tube. J Clin Pharm Ther 2018; 43: 730–2.
12 MSD. Procedures for Crushing Zepatier for NG or Stomach Tube Administration. 23 February 2017.
13 FDA. Zepatier: Clinical Pharmacology and Biopharmaceutics Review. 208261Orig1s000. 2015. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208261Orig1s000ClinPharmR.pdf.
14 EMA. Guideline on the Investigation of Bioequivalence. 2010.
15 FDA. Guidance for Industry: Statistical Approaches to Establishing Bioequivalence. 2001.
16 EMA. Guideline on Bioanalytical Method Validation. 2012.
17 van Seyen M, de Graaff Teulen MJA, van Erp NP et al. Quantification of second generation direct-acting antivirals daclatasvir, elbasvir, grazoprevir, ledipasvir, sitaprevir, sofosbuvir and velpatasvir in human plasma by UPLC-MS/MS. J Chromatogr B Analyt Technol Biomed Life Sci 2019; 1110-1: 15–24.
18 Howe AY, Black S, Curry S et al. Virologic resistance analysis from a phase 2 study of Mk-5172 combined with pegylated interferon/ribavirin in treatment-naive patients with hepatitis C virus genotype 1 infection. Clin Infect Dis 2014; 59: 1657–65.
19 EMA. Zepatier: Assessment Report. 2016. https://www.ema.europa.eu/en/documents/assessment-report/zepatier-epar-public-assessment-report_en.pdf.
20 Cheung TT, Yan Chiu JW, Yuen MF et al. A phase I, single- and multiple-dose study to evaluate the pharmacokinetics of elbasvir and grazoprevir in healthy Chinese participants. Clin Ther 2018; 40: 719–32.e1.