SHORT REPORT

Food intake and darunavir plasma concentrations in people living with HIV in an outpatient setting

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Received 9 December 2016; Revised 29 May 2017; Accepted 4 July 2017

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Keywords antiretrovirals, clinical pharmacology, HIV/AIDS, infectious diseases, patient safety, pharmacokinetics

AIMS
Patients receiving darunavir are advised to take it concomitantly with food. The objectives of the present cross-sectional study were to evaluate the actual concomitant food intake of patients visiting an HIV outpatient clinic.

METHODS
Sixty participants treated with darunavir/ritonavir once daily were subjected to a food recall questionnaire concerning their last concomitant food intake with darunavir. Darunavir trough concentrations were calculated.

RESULTS
The median food intake was 507 (0–2707) kcal; protein intake, 20 (0–221)g; carbohydrate intake, 62 (0–267)g; fat intake: 14 (0–143)g; and dietary fibre: 4 (0–30)g. Twenty-five patients (42%) ingested their drug with between-meal snacks. No relationship was found between food intake and trough concentrations.

CONCLUSIONS
Clear advice on the optimal caloric intake is needed, to avoid high caloric intake in patients who already have an increased risk of cardiovascular disease due to their HIV infection.

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DOI:10.1111/bcp.13366
WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- In healthy volunteers, administration of 400 mg darunavir in a fasting state has been shown to result in a peak plasma concentration and area under the curve decrease of approximately 30% compared with administration after a standard meal.
- No significant differences have been observed in darunavir plasma concentrations between the different diets tested.
- The advice on concomitant food intake in patient brochures varies highly in caloric intake.

WHAT THIS STUDY ADDS

- Concomitant food intake in a real-life outpatient setting varied greatly and was often unnecessarily high.
- A large number of people using darunavir take their drug with a between-meal snack.
- Healthcare providers and patient brochures should ensure that their advice on concomitant food intake does not contribute to an unhealthy diet.

Introduction

Darunavir (DRV) is a protease inhibitor (PI) that is administered with low-dose ritonavir (RTV) to provide a pharmacokinetic boost by inhibiting drug metabolism, thereby enhancing plasma concentrations over time [1]. Although DRV is considered to be a safe and efficacious drug, a considerable pharmacokinetic variability has been observed [2].

The observed variability may be partly explained by a food effect. In a prior study assessing the food effect on the bioavailability of DRV 400 mg (with RTV) in healthy volunteers, the bioavailability increased by 30% with food intake compared with the fasting state, and no significant differences were observed between the different diets tested [3].

Partly because of this food effect study, patients using DRV are advised to ingest their drug concomitantly with food. However, there is no clear-cut advice on how much nutritional content (e.g. number of calories, and amount of fat, protein and carbohydrate) a meal should contain. The patient product brochures seem to focus more on caloric intake—e.g. the Dutch National Food Consumption Survey 2016 was used as a reference, in addition to the questionnaire used, to determine the type of meal (breakfast, lunch or dinner, or a between-meal snack [7]). The food recall questionnaire was analysed by D.D. using EvryDietist, 6.2.9.9 (Nevo 2011 data, Evry bv, Alphen aan den Rijn, Netherlands). The following nutritional values were calculated: energy (kcal), protein (g), carbohydrate (g), total fat (g) and dietary fibre (g). During the second half of the study, four questions were added to the food recall questionnaire in order to optimize the interpretation of the food intake. The first three additional questions asked were:

1. Did your care providers advise you to eat concomitantly with DRV?
2. If yes, what food intake did your care providers advise?
3. What amount of food do you consider appropriate for intake concomitantly with DRV?

In the fourth question, we asked if patients changed their food pattern as a consequence of DRV and its concomitant food intake advice. We disregarded this question; interpretation of the answer was not possible without information on the antiretroviral therapy taken before the start of the DRV administration.
Pharmacokinetic assessment

Participants were asked at which time point DRV was ingested. The time of blood sampling was recorded. The concentrations of DRV in human plasma were analysed using a validated liquid chromatography–tandem mass spectrometry (LC–MS/MS) method. All analyses were performed on a Thermo Fisher Scientific Inc. (San Jose, CA, USA) triple quadrupole LC–MS/MS with a Finnigan™ Surveyor® LC pump and a Finnigan™ Surveyor® autosampler. The mobile phase consisted of an aqueous buffer (containing ammonium acetate 5 g l⁻¹, acetic acid 35 ml l⁻¹ and trifluoroacetic anhydride 2 ml l⁻¹ water), water and acetonitrile and had a flow rate of 0.3 ml min⁻¹. The calibration curves were linear within the concentration range 0.335–33.5 mg l⁻¹ for DRV and had a correlation coefficient (R²) of 0.999. The lower limit of quantification (LLOQ) for DRV was 0.27 mg l⁻¹. This method is precise and accurate: within-day precision ranged between 2.2% and 3.2% for DRV, and between-day precision from 3.0% to 5.2%. The calculated accuracy ranged from 0.0% to 11.8%.

The DRV C_{trough} was defined as the plasma concentration at 24 h after intake of the dose. To estimate the C_{trough}, we used a DRV iterative two-stage Bayesian population pharmacokinetic model using the software package MWPharm Research version 3.82 (Mediware, Groningen, the Netherlands) [8]. The model for DRV is a one-compartment model with input and elimination from the central compartment. Parameters for this model are: a volume of distribution of the central compartment of 2 l kg⁻¹ [standard deviation (SD) 0.5 l kg⁻¹], total body clearance of 6.3 l h⁻¹ 1.85 m² (SD 1.57 l h⁻¹ 1.85 m²), first-order absorption constant of 1 h⁻¹ (SD 0.25 h⁻¹) and a bioavailability of 0.8 (in combination with RTV). This model was built in-house and derived from data provided in the literature [9]. A median population pharmacokinetic curve was used as a cut-off value for follow-up as in standard care [10, 11]. A DRV C_{trough} below 1.07 mg l⁻¹ is an indication for follow-up, in accordance with the treatment protocol. The median population pharmacokinetic curve is seen as a cut-off value for the once-daily dosage and not as the minimally effective concentration.

Further, the medical records of all participants were studied for medication potentially influencing the DRV concentrations.

Statistical analysis and data processing

C_{trough} levels vs. the calculated kcal, carbohydrate, protein, total fat and dietary fibre values were presented in a scatter plot. Curve estimation tests were performed to find the best fit. All descriptive analyses were performed using SPSS for Windows, version 22.0 (IBM SPSS, Chicago, IL, USA).

Nomenclature of targets and ligands

Key ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [12].

Results

Participant characteristics

Sixty patients were enrolled, of whom 50 were male. Participant demographic characteristics are presented in Table 1. Forty-seven per cent of the participants were overweight [body mass index (BMI) ≥25 kg m⁻²], of whom 13% were classified as obese (BMI ≥30 kg m⁻²).

Nutritional analysis

The medians of the calculated nutritional values for the meal concomitantly ingested with DRV are shown in Table 2. Eleven participants ingested DRV with breakfast, even with lunch, 14 with dinner and three without concomitant food, and 25 participants took their DRV with a between-meal snack.

Twenty-eight (85%) of the participants interviewed about the advice received at start of the treatment confirmed that the care provider advised them to eat concomitantly with the ingestion of DRV. Twenty-four participants (73%) indicated that they did not know the amount of food intake recommended with DRV ingestion.

Pharmacokinetic analysis

The median (interquartile range) DRV C_{trough} for the 60 participants was 2.3 (1.51–3.67) mg l⁻¹. Seven participants (12%) had a DRV C_{trough} below the used cut-off value of 1.07 mg l⁻¹. No pattern could be detected in the DRV C_{trough} and the caloric intake. A biologically expected S-curve did not fit the data (P = 0.260), as presented in Figure 1. A linear model fitted slightly better compared with the other curve estimations but still showed no correlation (rho = −0.178, P = 0.173). Similar results were found for the other nutritional values (protein, carbohydrate, total fat and dietary fibre; not

Table 1

Baseline demographic characteristics of the 60 study participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>45 (20–66)</td>
</tr>
<tr>
<td>Median body mass index (kg m⁻²)</td>
<td>24.66 (16.80–39.18)</td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>50 male</td>
</tr>
<tr>
<td></td>
<td>10 female</td>
</tr>
<tr>
<td>Mean creatinine clearance (ml min⁻¹)</td>
<td>99 (46.1–166.0)</td>
</tr>
<tr>
<td>Median ASAT</td>
<td>29 (18–261)</td>
</tr>
<tr>
<td>Median ALAT</td>
<td>23 (10–784)</td>
</tr>
<tr>
<td>Mean CD4+ cell count</td>
<td>510 (130–1200)</td>
</tr>
<tr>
<td>Viral load (n = 44)</td>
<td>Undetectable</td>
</tr>
<tr>
<td>Median viral load (n = 16) (copies ml⁻¹)</td>
<td>92 (56–1340)</td>
</tr>
<tr>
<td>Duration darunavir use (months)</td>
<td>20 (0.50–59)</td>
</tr>
</tbody>
</table>

ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase
The use of antiretroviral therapy has been associated with a higher risk of cardiovascular and metabolic disorders, such as hyperlipidaemia, insulin resistance, metabolic syndrome and diabetes [13–16]. Therefore, it is important to ensure that the advice on concomitant food intake while using DRV does not lead to an unnecessarily higher caloric intake. Based on the findings by Sekar et al. [3] and our findings, we suggest that much of the food advice shown in the DRV patient brochures can be adapted to healthier dietary advice [4, 5].

Due to the observational nature of the study, it is possible that a recall bias on food intake was introduced, despite taking a careful history using a validated food recall questionnaire. Furthermore, the $C_{\text{trough}}$ was estimated using one blood sample, which could have given a distorted view. However, repeated blood samples would alter the actual (cross-sectional) study design, and the use of Bayesian estimation in combination with patient characteristics, dosage and time of ingestion is a widely accepted method in daily practice to interpret drug level results [8, 17]. Despite potential weaknesses, the results of the present study provide a good insight into the daily concomitant food intake in patients.

A controlled food effect study in patients is needed to optimize recommendations on the minimal amount of concomitant food intake to prevent unnecessary high-caloric and high-fat food intake in a patient group with already increased risks for cardiovascular and metabolic diseases.

Competing Interests

There are no competing interests to declare.

Contributors

A.D., W.F.W.B., J.G.W.K., J.W.C.A. and Y.S. were responsible for the concept and design of the study. The acquisition of laboratory and clinical data was performed by A.D., D.D., D.A.W. and T.S.W. The data was analysed by A.D. and Y.S. Both the drafting and the later critical revision of the article was conducted by A.D., T.S.W., J.W.C.A. and Y.S. The final approval of the manuscript was done by all authors.

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