Introduction

If HIV-patients are unconscious or cannot swallow tablets for other reasons, antiretroviral medication is often crushed and dissolved prior to administration. Crushing can influence pharmacokinetics (PK) leading to altered drug exposure, possibly leading to treatment failure, development of resistance or toxicity.

Currently there is no information about crushing the brand fixed-dose combination of dolutegravir (DTG) / abacavir (ABC) / lamivudine (3TC) (TRI)®, therefore crushing TRI is not recommended.

PK interaction between DTG and enteral nutrition is possible, based on the known interaction between DTG and cations in antacids and dietary supplements.

Objective

To investigate whether the branded fixed-dose combination tablet of dolutegravir/abacavir/lamivudine can be crushed and combined with enteral nutrition without influencing pharmacokinetics.

Material & Methods

• This was an open-label, 3-period, randomized, single-dose, cross-over, trial in 22 healthy volunteers.
• Subjects received the following three treatments below in a random order:
  - Reference treatment; TRI whole tablet fasted,
  - Intervention I; crushed and suspended TRI fasted,
  - Intervention II; crushed and suspended TRI with 250 mL enteral nutrition (Nutrisource®) taken orally.

Between the different treatment periods a wash-out period of 7 days was scheduled. The tablet was crushed using a tablet crusher (figure 1).

• A 48-h PK profile was measured for all compounds. Geometric mean ratios (GMR) with 90% confidence interval (CI) for ABC and DTG were calculated for intervention I and II versus the reference treatment. Bioequivalence was accepted when the 90% CI was within 80-125%. Safety and tolerability were evaluated.

Results

• 22 healthy volunteers (21 Caucasian and 1 mixed-race, 10 female), 25 (18-54) years old and BMI 23 (20-27) kg/m² (median; range) were included.

• Intervention I vs. reference treatment; a crushed tablet is not bio-equivalent to the whole tablet, since DTG AUCinf and Cmax increased with 26% and 30% respectively (see figure 1) and the corresponding 90% CIs of GMRs fell outside the predefined bio-equivalence range of 80-125% (Table 1). For ABC and 3TC the GMRs and 90% CI for AUCinf and Cmax fell within 80-125%.

• Intervention II vs. reference treatment; for the crushed tablet with enteral nutrition (figure 2), DTG Cmax increased with ca. 21% compared to the whole tablet fasted. ABC Cmax decreased with 17% (see table 1).

• The 90% CIs of GMRs for Cmax of both DTG and ABC comparing a crushed TRI tablet with enteral nutrition to a whole tablet TRI, fell outside the predefined bio-equivalence range and therefore bio-equivalence could not be demonstrated (see Table 1).

Table 1: PK-parameters for dolutegravir, abacavir and lamivudine GMRs.

<table>
<thead>
<tr>
<th>PK-parameter</th>
<th>Reference treatment (swallowed tablet, fasting)</th>
<th>Intervention I (crushed tablet, fasting)</th>
<th>Intervention II (crushed tablet, mixed with enteral nutrition)</th>
<th>Intervention II vs. reference treatment (ABC 90% CI)</th>
<th>Intervention II vs. reference treatment (DTG 90% CI)</th>
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<tbody>
<tr>
<td>DTG</td>
<td>AUCinf (mg·h/L)</td>
<td>0.86 (0.78-0.94)</td>
<td>0.81 (0.72-0.92)</td>
<td>0.79 (0.70-0.89)</td>
<td>0.80 (0.71-0.90)</td>
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<td>Cmax (mg/L)</td>
<td>4.88 (4.11-5.91)</td>
<td>4.79 (4.12-5.61)</td>
<td>4.68 (4.00-5.51)</td>
<td>4.77 (4.10-5.63)</td>
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<td>T1/2 (h)</td>
<td>1.08 (0.93-1.26)</td>
<td>1.06 (0.92-1.22)</td>
<td>1.04 (0.90-1.20)</td>
<td>1.05 (0.91-1.19)</td>
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<td>T1/2 (h)</td>
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</table>

Conclusion

In our opinion TRI can be crushed for patients with swallowing difficulties or with an enteral feeding tube and can be combined with enteral nutrition without separating intake in time. Although no dose-limiting toxicity of DTG is observed to date, crushing dolutegravir is advised against if BID dosing and intake with food is needed.

ACKNOWLEDGEMENTS

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REFERENCES