Influence of capecitabine absorption on its metabolites pharmacokinetics: a bioequivalence study

The clinical interest of capecitabine (Xeloda®, Roche) administration lies in the areas of safety, quality of life, oral administration and shorter duration of hospitalisation [1, 2]. However, patients unable to swallow the tablets cannot benefit of this oral prodrug. To tackle this issue, we studied bioequivalence between crushed tablets and plain capecitabine tablets.

Fourteen cancer patients were included in two arms of a randomised, single-centre intrapatient crossover phase I trial: regular commercial tablets on day 1 (1250 mg/m² b.i.d.), then crushed regular commercial tablets on day 2 in the first arm and the opposite in the other arm. The administration of crushed tablets was carried out after dispersion in 40 ml of water. Eight pharmacokinetic samples were taken each morning during 6 h. Measurement of capecitabine and metabolites [5′-DFCR (5′-deoxy-5-fluorocytidine), 5′-DFUR (5′-deoxy-5-fluorouridine) and 5-fluorouracil (5-FU)] was carried out by HPLC with UV detection. Exposure was (AUC0–6) calculated by trapezoidal method, maximal concentration (Cmax), time to Cmax (Tmax) and apparent elimination constant (ke).

Bioequivalence is defined as the relative 90% confidence interval (CI90) between 80% and 125% of the geometric mean as compared with the reference formulation [3]. A two-way analysis of variance with ‘sequence’, ‘period’, ‘treatment’ and ‘patients in treatment effects was applied to estimate the residual variance used for the calculation of CI90, whereas ke, and Tmax were compared using paired nonparametric comparisons (Wilcoxon test).

High interindividual variability was observed with all compounds independent of the given galenic formulations (Figure 1). The administration of the crushed tablets resulted in statistically faster and more extensive absorption without modification of elimination process (ke) for all molecules. Interestingly, the study of individual pharmacokinetic profiles showed that the profiles of the metabolites, including 5-FU, followed that of capecitabine, indicating that its absorption is of great importance for the production and kinetics of these metabolites. Together with the variability of enzymes implied in 5-FU metabolism (thymidine synthase, dihydropyrimidine dehydrogenase, thymidine phosphorylase), this variability might suggest the potential need to perform therapeutic drug monitoring (TDM) in patients treated by capecitabine.

For all compounds, bioequivalence was observed for area under the curve (AUC), but not for Cmax. For instance, the ratio between the AUC and the Cmax of the two formulations was, respectively, 101.1% (88.0% to 116.2) and 153.6% (1,093–2,159) for capecitabine and 94.6% (82.8% to 108.2) and 164.3% (119.1% to 226.7%) for 5-FU. The crushing of the regular tablets induced a faster and a more extensive absorption of capecitabine and, as previously mentioned, all metabolite pharmacokinetics are influenced by this absorption (Figure 1). Nevertheless, the AUC0–6 remained comparable and bioequivalence could be reached for this major parameter. We thus think that capecitabine crushed tablet-based treatments could be administered without dose adaptation allowing an extension of the use of capecitabine. Indeed, AUC is the main parameter used to assess and monitor toxicity, tumour response or survival [4]. Administration of crushed tablets of capecitabine can be suitable for patients unable to swallow tablets. Attention should be nevertheless paid regarding the potential need for TDM due...
to the high impact of capecitabine absorption on the pharmacokinetics of metabolites.

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