

Assessment of age-related Changes in Pediatric Gastrointestinal Solubility of Clarithromycin in Biorelevant Media

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Abstract

Background: Solubility of a drug in the gastrointestinal (GI) tract is an important determinant of its oral bioavailability as only dissolved drugs are absorbed from the GI tract. Adults and children have different physiological and anatomical characteristics, which consequently may lead to differences in the pharmacokinetics of drugs and consequently lead to different exposure-response. Paracetamol is widely used as an antipyretic and analgesic for the treatment of fever and pain in pediatrics because of its known efficacy and favorable safety profile. Solubility of paracetamol in pediatric biorelevant media was not assessed before.

Objective: The aim of the study was to assess the solubility of paracetamol in biorelevant pediatric media and compare it with the relevant adult compounds.

Methods: Solubility of paracetamol was assessed in 13 biorelevant media reflective of the gastric and proximal small intestinal environments in both fasted and fed states. Solubility assessment was conducted in a shaking water bath with a temperature set to 37 °C and 200 strokes/min. Solubility assessments were determined following a 72 h dwell period. Saturated media samples were then filtered through 0.45 µm cellulose filters and diluted with fresh media before analysis. Assessment of solubility in the fed-state media was conducted using equilibrium dialysis using dialysis membrane (MWCO 12,000–14,000 Da). For solubility assessment, dialysis membranes were removed and their contents were extracted, vortexed, centrifuged at 8,000 rpm and 4 °C for 15 min, and then filtered through 0.45 µm cellulose filters. Quantification of paracetamol was done using HPLC.

Results: In the simulated fasted-gastric media, solubility of paracetamol significantly decreased in biorelevant media representative of both neonates and infants. In fasted-state intestinal media, solubility was increased in media representative of pediatric media when the bile salts were assumed 50% of those of adults. Interestingly, solubility ratios were within the 80%-125% criteria which indicated that the differences in solubility of paracetamol in pediatric media compared to adult media were within the acceptable range.

Conclusions: Although the solubility of paracetamol was different in pediatric biorelevant media compared to those in adults, interestingly, it did not fall outside an 80-125% range from adult

values in pediatric media. Findings of this study suggest slight age-related changes in solubility of paracetamol in relation to the GI fluid composition. More investigations are needed to define a future pediatric biopharmaceutical classification system as pediatric biopharmaceutics are not well understood