DOSE EVALUATION OF INTRAVENOUS METAMIZOLE (DIPYRONE) IN INFANTS AND CHILDREN: A PROSPECTIVE POPULATION PHARMACOKINETIC STUDY

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Background The prodrug metamizole is frequently dosed intravenously (IV) for postoperative pain in children of all ages, despite its off-label use in infants < 1 year. We aimed to investigate the pharmacokinetics (PK) of the main metabolite of metamizole, 4-aminoantipyrine (MAA), in children aged 3–72 months following IV dosing. Methods 10 mg/kg metamizole was administered IV for postoperative analgesia. PK samples were drawn at 5 predefined time points. PK of the main active metabolite MAA and three other metabolites was characterized by both non-compartmental (NCA) and population PK analysis (PPK). AUC0-inf of MAA was calculated by NCA for two age cohorts (3–23 months, 2–6 years) and compared to the 80–125% range of adult dose-adjusted reference exposure (AUCref). PPK investigated age and weight dependency of the kinetics, and dosing strategies to achieve equivalent adult exposure in children. Results A total of 25 children aged 5 months – 5.8 years (7.8–24.8 kg) with at least one plasma concentration sample were included in PPK, 19 children who had 5 predefined samples up to 10 h post-dose were included in NCA. AUC0-inf of MAA in children of 2–6 years was 29.8 (95%CI 23.3–38.1) mg/L*h, significantly lower than AUCref(80%–125%) range: 39.2–61.2 mg/L*h). AUC0-inf of MAA in infants of 3–23 months was 42.5 (95%CI 15.7–115.4) mg/L*h, overlapping with AUCref. The large variability observed in infants could be partially explained by covariates body weight and age.

Conclusions Kinetics of the main active metabolite MAA depends on age in infants and children. MAA exposure after a single IV dose of 10 mg/kg metamizole in infants < 1 year of age was higher compared to an equal dose in adults and older children. This suggests that the optimal dose for this age group to achieve equivalent exposure compared to adults is lower than currently recommended.

Disclosure(s) Nothing to disclose.