The Interaction between Sildenafil and Phenobarbital in Infants with Congenital Heart Defects

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Introduction: Sildenafil, a substrate of CYP3A, is routinely used in children with pulmonary arterial hypertension (PAH) due to congenital heart defects (CHD). The current dosing recommendation for sildenafil in children is 0.5-2.0 mg/kg three times a day. The objective of this study was to assess the interaction between sildenafil and phenobarbital using opportunistic blood sampling during routine in-patient treatment of children younger than 2 years of age. Methods: After obtaining informed consent, remnant blood samples were analysed, using a validated LC-MS/MS assay, if collected within 8 h after the last oral sildenafil administration. In addition, patient characteristics, diagnoses, and co-medications in order to screen for drug interactions were extracted from the medical records. Plasma concentrations obtained this way were compared with those of traditional studies in children using planned serial sampling. Results: Nineteen patients (10 males) with a median age of 7.1 months (range 4 days- 15.6 months), and median weight of 6.2 kg (3.05-8.0 kg) were included. Mean pulmonary artery pressure was 31 ± 14 mmHg during therapy. In total, 266 blood samples were collected (3-43 samples per patient). Maximum sildenafil concentration ranged from 2.80-645 ng/ml (median Cmax 91 ng/ml), median time of maximum plasma concentration (Tmax) was 1.92 h. Mean administered dose was 0.86 mg/kg (0.45-1.95 mg/kg) three or four times a day. Fourteen patients were co-treated with the CYP3A inducer phenobarbital. If available, phenobarbital concentrations ranged from 15-47 mg/L (median 30.7 mg/L). There was no significant difference in sildenafil dose (0.97 ± 0.47 mg/kg vs. 0.69 ± 0.23 mg/kg, p=0.25), or Tmax (2.1 ± 1.5 h vs. 1.9 ± 2.3 h, p=0.51), but in Cmax normalized to dose (34.9 ± 55.1 ng/mL/mg vs. 79.6 ± 45.4 ng/mL/mg, p=0.03) between the patients who received short-term phenobarbital therapy and those who did not. Conclusions: The mean sildenafil dose matches the recommended dose range of 0.5-2.0 mg/kg. Sildenafil plasma concentrations show substantial inter-patient variability during exposure to therapeutic concentrations of phenobarbital, but the extent of CYP3A induction in infants still remains to be studied. The correlation between plasma and effect site concentrations and the predictive value of plasma concentration measurements of sildenafil, however, still have to be investigated in children.