P-221

Sildenafil Plasma Concentrations during Routine Treatment of Children with Pulmonary Arterial Hypertension

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Introduction: Sildenafil, a substrate of CYP3A, is a treatment standard of children with pulmonary arterial hypertension (PAH). The current dosing recommendation for sildenafil in children is 0.5-2.0 mg/kg thrice daily. The objective of this study was to generate a dataset of sildenafil plasma concentrations during routine in-patient treatment in infants and children with PAH using opportunistic blood sampling for pharmacokinetic analysis.

Methods: After obtaining informed consent, sparse remnant blood samples from routine blood analyses were analyzed if drawn within 8 h after the last oral sildenafil administration using a validated LC/MS/MS assay. In addition, patient characteristics, diagnoses, and comedications in order to screen for drug interactions were extracted from the medical records. Obtained plasma concentrations were compared with those of traditional studies in children using serial sampling.

Results: Twenty-two patients (11 males) with a median age of 7.5 months (range 4 days- 9.5 months), median weight of 6.54 kg (3.05-26.7 kg) were included. Twenty-two patients had pulmonary hypertension associated with congenital heart disease and two had other causes. Mean pulmonary artery pressure was 29 ± 14 mmHg during therapy. Seven patients were classified as Rosenthal class B and 15 were class C. In total, 271 blood samples were collected (3-38 samples per patient). Maximum sildenafil concentration ranged from 2.80 to 645 ng/ml (median Cmax 87.4 ng/ml), time of maximum plasma concentration (Tmax) ranged from 0.1 to 5 h after dosing (median 2 h). Median administered dose was 0.86 mg/kg (0.45-1.95 mg/kg) three or four times a day. Cmax normalized to dose was 0.99-215 ng/ml/mg. Eleven patients were co-treated with the CYP3A inducer phenobarbital.

Conclusions: The mean sildenafil dose matches the recommended dose range of 0.5-2.0 mg/kg. Plasma concentrations using remnant samples were comparable to those of previously conducted pediatric studies, indicating rapid elimination in children. Sildenafil plasma concentrations showed substantial inter-patient variability; the correlation between plasma and effect site concentrations and the predictive value of plasma concentration measurements, however, still have to be investigated in children, as well as the extent of CYP3A induction by phenobarbital in children.