K59 Pyrimethamine Toxicity: A Case Report

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After attending this presentation, attendees will understand the pharmacology and toxicology of pyrimethamine.

This presentation will impact the forensic science community by offering a description of the analysis of biological and non-biological material for pyrimethamine, a drug not normally encountered in routine forensic casework. In addition, a brief review of published cases involving pyrimethamine toxicity and a case report of an infant showing symptoms of pyrimethamine toxicity will be provided.

Pyrimethamine (PYR) is an antiparasitic medication used for treatment of protozoal infections including toxoplasmosis. The recommended dose for treatment of congenital toxoplasmosis is 1mg/kg/day for two to four days, then 0.5mg/kg/day for one month. Peak plasma concentrations following doses of 0.5-2mg/kg/day were 0.29-2.2mcg/mL with half-lives of 2.7-5.2 days. Plasma concentrations in previously reported cases involving toxicity in infants were 1.5, 6.2, and 13.0mcg/mL. Adverse effects associated with pyrimethamine treatment include anorexia, rash, and hematological disorders including bone marrow depression. Concurrent administration of folic acid has been used to minimize the risk of reversal neutropenia that has been noted in infants undergoing pyrimethamine treatment. PYR toxicity characterized by neurological hyper-excitability, seizure, and gastrointestinal symptoms has rarely been reported.

In this case, a five-month-old male child, on therapy for congenital toxoplasmosis complicated by chorioretinitis, developed irritability and was seen in an emergency room and discharged after receiving a single dose of PYR. Shortly after a second dose, he developed irritability and suffered a tonic-clonic seizure. The seizure responded to lorazepam administration and he was admitted to the hospital. PYR was stopped for 24 hours and no seizures were noted. Upon re-introduction of the medication from the same dispensed bottle, the child suffered another seizure. Serum samples collected 18 hours, 4 days, and 11 days after last exposure were analyzed for pyrimethamine along with the liquid medication used to treat the infant.

PYR was quantified in serum using a validated assay. Samples underwent a three-step liquid-liquid extraction, and then were dried, reconstituted in toluene, and derivatized with butyric anhydride. Samples were then injected on the gas chromatograph with a nitrogen phosphorus detected and separated on a DB-17 capillary column (15m x 0.32mm I.D., 0.15mcm film) using a temperature gradient and constant gas flow. The serum specimen, collected ~18 hours after the last dose, contained 3.8mcg/mL PYR. Four days later, PYR concentration had dropped to 1.2mcg/mL and 11 days post-exposure the PYR was below the reporting limit of the assay (0.2mcg/mL). The liquid medication, which was supposed to contain 2mg/mL PYR, was determined to have a concentration of 94mg/mL. Based on the calculated concentration in the medication the infant received, approximately 280mg of PYR instead of 6mg ((based on the prescribed dose of 3mL of a 2mg/mL solution). Despite the long half-life of PYR, it can still be assumed that the peak concentration of PYR would have been achieved well before this serum was collected so it would have been greater than 3.8mcg/mL and in the range of previously reported toxicities. The concentration of 1.2mcg/mL four days later is consistent with the reported half-life of PYR.

Pyrimethamine, Pediatric, Toxicology