K20 Pharmacokinetic Postmortem Evaluation Reveals Death of a Toddler From Carbamazepine to be Accidental Rather Than Criminal

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After attending this presentation, attendees will understand principles of clinical pharmacokinetics regarding the concentrations of carbamazepine that would be expected in its treatment of epilepsy. These include the effect of dosage changes, interactions with drugs that induce carbamazepine metabolism, and drugs that inhibit carbamazepine metabolism. Knowledge of dosage changes and drug interactions provide critical insight for interpretation of toxic concentrations measured at time of autopsy.

The presentation will impact the forensic science community by providing an understanding of how pharmacokinetic variables can affect relationships between dose and concentrations can provide insights for interpretation of toxic concentrations

Carbamazepine and phenytoin are two antiepileptic drugs that are prescribed for both partial seizures and generalized tonic clonic seizures.[1] These two drugs require therapeutic drug monitoring during treatment to ensure efficacy and prevent undesired adverse effects. When administered concomitantly, there is potential for a pharmacokinetic drug-drug interaction to occur. Rare cases of toxicity due to concomitant administration have been reported in the literature. Described herein are the circumstances and autopsy findings of a 23-month old child with a history of epilepsy whose death was caused by acute carbamazepine intoxication. This child suffered from seizure disorder since the age of one. Because of an intolerability to phenobarbital and mephobarbital (two other antiepileptics), he was placed on carbamazepine and phenytoin. The child died five months later and the cause of death was determined to be carbamazepine toxicity. The postmortem serum concentration of carbamazepine was 23.7mcg/ml, which is significantly higher than targeted therapeutic levels of 5-12mcg/ml.[1] The toddler's caregiver was then alleged to have intentionally overdosed the child causing acute toxicity, but events leading up to the death of this child included a myriad of dosing changes including discontinuation of phenytoin two weeks prior to the time of death.

Carbamazepine is converted to an active metabolite, carbamazepine 10,11-epoxide, through oxidation which is then metabolized to carbamazepine diol, the inactive metabolite.[2] Phenytoin is a potent inducer of the liver enzyme CYP3A4, which predominantly metabolizes carbamazepine, causing higher carbamazepine epoxide/carbamazepine and carbamazepine diol/carbamazepine ratios in children receiving both drugs.[2-3] A decrease in plasma concentrations of carbamazepine is correlated with the dosage of phenytoin being administered.[4-5] Also, because carbamazepine has a unique property of auto-induction, the dose is increased gradually based on serum levels drawn every two to four weeks after initiation of therapy.[1] Average steady state concentrations of carbamazepine decrease by 50% after three weeks of administration.[6] A study conducted by Duncan et al. observed the effects of phenytoin discontinuation on concomitant carbamazepine therapy. It was found that upon discontinuation, total carbamazepine concentrations increased by a mean of 48% after four weeks of phenytoin removal and the ratio of carbamazepine epoxide/carbamazepine decreased.[7]

During the five months prior to death, the child's carbamazepine dose was increased from 150mg/day to 500mg/day. Over this same period of time the child was also treated with medications that can alter the pharmacokinetic disposition of carbamazepine. Pharmacokinetic modeling was used to estimate expected carbamazepine serum levels based on carbamazepine dosing orders from the time carbamazepine was started, the known effects of concomitant drugs on the pharmacokinetic disposition of carbamazepine and the timing of the addition and/or removal of these other drugs. Estimates of carbamazepine concentrations from the pharmacokinetic model were compared to actual measured concentration. Estimated concentrations correlated well with measured concentrations. This demonstrated that carbamazepine concentrations measured at autopsy were the concentrations expected based on the dosing history and timing of the addition and removal of other drugs known to effect the pharmacokinetics of carbamazepine. The concentrations of carbamazepine measured at autopsy were concentrations were expected concentrations based on the prescribed doses as predicted by the pharmacokinetic model. Deliberate overdosing of carbamazepine was ruled out and with this insight the child's caregiver was exonerated.

This case underscores the importance of understanding the pharmacokinetic history of drugs with narrow therapeutic indices in the interpretation of toxic drug concentrations measured at autopsy.

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Carbamazepine, Toxicity, Postmortem Drug Levels

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