K37 Topiramate (Topamax®) Positive Death Investigation and Impaired Driving Cases in Washington State

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After attending this presentation, attendees will understand that topiramate is increasingly prescribed for seizure disorders and off-label use. This presentation gives context for evaluation of topiramate blood concentrations in two populations, death investigation cases, and suspected impaired drivers.

This presentation will impact the forensic community and/or humanity by providing information as to the topiramate concentrations detected in two populations, death investigations and suspected impaired drivers, and will assist other forensic toxicologists in interpreting the level of this drug in their own cases.

Topiramate (Topamax®) has been available since 1996 and has proven very effective for treating seizure disorders. As with many other anti-epileptic drugs (AED), topiramate has recently gained attention for its off-label use. A search in PubMed® disclosed articles describing topiramate use for the treatment and prevention of migraines, cluster headaches and childhood headaches; psychosis, mania, schizophrenia, bipolar disorder, depression and kleptomania; eating disorders including bulimia, binge eating obesity, anorexia nervosa, and as adjunct therapy to treat weight gain with olanzapine, SSRIs and other anti-psychotic medications; neuropathic pain; alcohol dependency and craving, morphine dependency; and benzodiazepine withdrawal. One article even described its use in treatment of refractive scars.

The effects of topiramate are concentration dependent and according to the manufacturer, not subject to the development of tolerance. Dosage for anti-seizure therapy ranges from 200 to 800 mg/day. Side effects include sedation, dizziness, ataxia, speech difficulty, nystagmus, and paresthesia. Metabolic acidosis has been reported in 2 cases.

Peak plasma concentrations in patients stabilized on 800 mg/day have been reported at 5.5 mg/L. Blood/plasma ratios are inversely proportional to concentration averaging 7.1 at a blood concentration of 3 mg/L and 1.3 at a blood concentration of 15 mg/L.[1] Mozayani *et al.*[2] reported a topiramate overdose with blood levels of 8.9 mg/L, and Langman *et al.*[3] reported a fatal topiramate toxicity with a postmortem central blood concentration of 170 mg/L.

In an effort to evaluate the role of topiramate in human performance and death investigation casework, the authors reviewed the findings in all positive topiramate cases from 1998 to June 2004.

Topiramate was first detected in a death investigation case in 1998. Since then the authors have reported 107 cases positive for topiramate; 51 death investigations, 55 suspected impaired drivers and 1 sexual assault. The subjects were predominantly female (71%) and had a median age of 40 (mean of 41). The median blood topiramate concentration was 6.2 mg/L (mean 10.8 mg/L, range 1-180 mg/L).

In the subset of death investigation cases, the mean and median age was 40 (range 12 to 63) and 61% were female. The median blood topiramate concentration was 6.6 mg/L (mean 15.2 mg/L, ranged 1.25 to 180 mg/L). At least one other drug was detected in 94% of the death investigations and 91% of the drivers. In one case, an 18 year old, female with one prior suicide attempt, was found unresponsive by her father. She was prescribed topiramate, quetiapine and bupropion for bipolar disorder. Numerous capsules and empty pill bottles were discovered at the scene. Toxicological analysis revealed: topiramate 180 mg/L, quetiapine 34.9 mg/L, bupropion 0.12 mg/L, bupropion metabolite 1.56 mg/L, and atomoxetine 1.55 mg/L. The cause of death was ruled a combined quetiapine and topiramate toxicity and the manner of death was a suicide.

In the driving subset, there was a higher incidence of females (80%) and the median blood topiramate concentration was 6.1 mg/L (mean 6.7 mg/L, range 1 -20.4 mg/L).

One of the driving cases involved a 40-year-old male city bus driver. He had developed a seizure disorder in 1999, had corrective brain surgery in 2001 and was subsequently prescribed topiramate and lamotrigine. He was concerned that topiramate affected his ability to process information, caused him to respond slowly and made multi-tasking difficult, and had complained to his physician. Despite his complaints, his physician wrote a letter in support of his reinstatement as a driver even while trying to wean the subject from his topiramate. In December 2003, the subject struck and killed a co-worker in the bus yard. The driver was evaluated by a drug recognition expert (DRE). During the evaluation he slurred his words and was noted to have coordination and balance difficulties. The DRE conclusion was that the subject was under the influence of a CNS depressant. The toxicological findings revealed lamotrigine concentration of 6.6 mg/L and a topiramate concentration of 3.7 mg/L. What is the conclusion regarding the significance of both drugs here? Any interaction?

Information on blood concentrations of topiramate is scant. This review of 107 cases including both death investigations and suspected impaired drivers found the median blood concentrations to be

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approximately 6 mg/L in both populations, and identified cases in which topiramate was implicated as the principle causative agent in deaths, and played a role in causing driver impairment.

References:

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Topiramate, Death Investigation, Imparied Driver

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