K25 The Toxicological Significance of Tramadol in Death Investigation and Impaired Driving Cases

Jayne E. Thatcher, BS, Washington State Toxicology Laboratory, Forensic Laboratory Services Bureau, Washington State Patrol, Seattle, WA; J. Matthew Lacy, MD, and Corinne L. Fligner, MD, Department of Pathology, University of Washington Medical Center, Seattle, WA; Norman Thiersch, MD, Snohomish County Medical Examiners Office, Everett, WA; John Howard, MD, Pierce County Medical Examiners Office, Tacoma, WA; Richard Harruff, MD , King County Medical Examiners Office, Seattle, WA; and Barry K. Logan, PhD, Washington State Toxicology Laboratory, Forensic Laboratory Services Bureau, Washington State Patrol, Seattle, WA*

After attending this presentation the participant will be able to assess the toxicological significance of a positive finding of Tramadol (Ultram®). Tramadol is a synthetic opioid-receptor agonist that exerts additional effect by inhibiting the reuptake of norepinephrine and serotonin. It has been used in the United States since 1995. Clinically it is used to treat moderate to severe pain. It is reported to have minimal abuse potential, and only mild side effects. Tramadol taken alone has been reported to be a relatively safe drug. However, due to its mode of action it could be potentially lethal when taken in excess or taken together with drugs acting on the same neurochemical or metabolic pathway.

This work was conducted as part of an assessment of the increasing incidence of analgesic drugs in the death investigation casework in the State of Washington between 1995 and 2000. Drug concentrations were assessed relative to accepted therapeutic ranges, and compared to concentrations encountered in drivers arrested for apparent impaired driving. Patterns of drugs found in combination with tramadol were assessed to identify possible pharmacokinetic and pharmacological interactions.

To perform this assessment, we obtained toxicological data from all death investigation cases in which tramadol was present, and matched it with public health data listing the certified cause and manner of death (n=72). All cases were tested at the Washington State Toxicology Laboratory for alcohol and screened for general drugs of abuse. Confirmation and quantitation of tramadol and other drugs was performed by gas chromatography/mass spectrometry. Additionally, investigative and autopsy data were obtained from the three largest counties in the state, and were used to examine the circumstances of death, and pathological features associated with a subset (n=40) of these cases. The toxicological data from a series of DUI cases occurring over the same period (n=39) were also considered This was used as a control group (living subjects) to assess postmortem drug concentrations and drug combinations. Literature on clinical trials of tramadol was also reviewed to assess normal patterns of prescribing and blood concentrations.

We observed a significant upward trend in the number of deaths certified in Washington State, involving tramadol, increasing from 5 cases in 1995, to 24 cases in 2000. The concentrations observed in death investigation cases ranged from <0.05 to 22.2 mg/L (mean: 2.06 mg/L, standard deviation: 4.02, median: 0.68mg/L). Toxicological literature states the therapeutic range to be 0.28-0.50 mg/L. For comparison, concentrations in suspected impaired drivers ranged from <0.05 to 5.36 mg/L (mean: 0.45 mg/L, standard deviation 0.94, median:0.15 mg/L). The most frequently observed manner of death was accidental (44%, 84% of which were "drug caused deaths") followed by natural (21%) suicide (18%, 77% of which were "drug caused deaths") and undetermined (12%, 92% of which were "drug caused deaths").

Tramadol was invariably ingested in combination with other drugs. In our data set there were no cases in which the cause of death was attributed to tramadol alone. Almost seventy percent of the cases were classified by the Department of Public Health as death attributed to drug(s). In those cases, other drugs were present in every instance. Morphine was the drug most frequently taken in combination with tramadol, closely followed by amitriptyline, its metabolite nortriptyline, nordiazepam, acetaminophen, trazodone, and carisoprodol. Over half of the decedents (66% of the "drug caused deaths" and 55% of the non-drug caused deaths) were taking an antidepressant in conjunction with tramadol. Similar patterns were observed in the drivers in whom antidepressants were present in 38% of cases. There were several cases in which death was attributed to the combination of tramadol with other drugs affecting the reuptake of serotonin. These included tricyclic antidepressants, and the selective serotonin reuptake inhibitors (SSRI's) fluoxetine, and sertraline. As tramadol itself inhibits serotonin reuptake, this raises the possibility of a serotonergic crisis (e.g. serotonin syndrome) contributing to the actual mechanism of death. Another concern is a metabolic interaction between tramadol and amitriptyline, which are both metabolized by the cytochrome P4502D6 enzyme. This combination may contribute to an elevation of tramadol concentrations even with therapeutic administration.

Our data show that tramadol does appear to be a fairly safe drug when taken alone, and that patients can survive concentrations in considerable excess of the accepted therapeutic concentration, albeit with significant apparent psychomotor effects on motor skills. Patterns of prescribing of tramadol still appear to include the co-administration of drugs that may have significant metabolic or pharmacological interaction, and these should be carefully considered when interpreting postmortem toxicological data.

Tramadol, Drug Interaction, Postmortem Toxicology

 ** Presenting Author*