K6 Benzodiazepine Effects on Opioid Parent and Parent-to-Metabolite Concentrations

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After attending this presentation, attendees will be able to characterize the parent drug to metabolite ratios for fentanyl, hydrocodone, methadone, and oxycodone in the presence and absence of benzodiazepines and note potential differential effects of alprazolam and diazepam on blood opioid concentrations in unintentional deaths.

This presentation will impact the forensic science community by contributing to the understanding of the possible interactions between benzodiazepines and opioids in unintentional drug deaths and assisting in the interpretation of parent opioid and metabolite concentrations during death examinations.

Drug overdose deaths involving opioids are a major health concern. They typically involve multiple drugs, with benzodiazepines (usually diazepam or alprazolam) frequently present. Many toxicology laboratories routinely measure parent drug and metabolite concentrations in poisoning deaths. The parent drug to metabolite ratio can help determine whether a drug overdose was acute, the manner of death, abuse/misuse vs. therapeutic drug use, or to differentiate between ingestion of a drug vs. an active metabolite that is also a prescribed drug. Few studies have examined postmortem blood opioid concentrations and parent drug/metabolite ratios in combination opioid-benzodiazepine deaths. Such studies can better characterize the range of values found and whether the opioid parent drug/metabolite ratio might be affected by benzodiazepines.

A Forensic Drug Database (FDD) was initially created to capture West Virginia (WV) drug death data. A project funded by the WV Injury Control Research Center's Centers for Disease Control and Prevention (CDC) renewal grant will expand the FDD to the Northern New England (NNE) states. Decedent data entered into the FDD includes demographic information, body condition, Body Mass Index (BMI), death certificate data, route of drug administration, whether a prescription was present for controlled substances identified, medical history, key autopsy findings (all decedents), and toxicological analyses (for all drug-related deaths). The database currently contains information on 2,784 WV drug-related deaths from January 2005 through most of 2010 (data entry ongoing); data from NNE are being compiled.

This study evaluated postmortem peripheral blood concentrations of parent drug and parent/metabolite concentration ratios of four opioids that are at least partially metabolized by Cytochrome P450 3A4 (CYP3A4): fentanyl/norfentanyl; hydrocodone/dihydrocodeine (metabolite most commonly measured); methadone/EDDP; and oxycodone/oxymorphone, in the presence and absence of co-intoxicant benzodiazepines, alprazolam, and diazepam. Due to potential competition for, or inhibition of, CYP3A4 by alprazolam or diazepam, the opioid parent drug concentrations and parent-to-metabolite ratios might be expected to be higher in the presence of these benzodiazepines compared to their absence.

All accidental WV overdoses involving $\leq$4 concomitant drugs (to reduce possible confounding) and in which fentanyl, hydrocodone, methadone, or oxycodone caused or contributed to death were identified. Cases were excluded if >1 opioid was present or if benzodiazepines other than alprazolam or diazepam were found (Dataset A: fentanyl (n=135); hydrocodone (n=135); methadone (n=337); oxycodone (n=270)). For parent drug and concentration ratio analyses in the presence/absence of benzodiazepines, cases with co-intoxicants that were inhibitors or inducers of CYP3A4 or Cytochrome P450 2D6 (CYP2D6) or that had documented pharmacokinetic interactions with opioids were further excluded (Dataset B: fentanyl (n=56); hydrocodone (n=49); methadone (n=166); oxycodone (n=78)).

Median concentrations were used for analyses. A summary of key findings follows. As the number of concomitant drugs increased, hydrocodone, methadone, and oxycodone concentrations significantly decreased. Statistically significant reductions in fentanyl and methadone concentrations (42% and 44%, respectively) were found when decedents lacked a valid prescription for that drug compared to when one was present (Dataset A). Only hydrocodone parent concentrations were significantly different overall in the presence or absence of benzodiazepines. Co-ingestion of alprazolam or alprazolam + diazepam were likely responsible (reductions of 34% and 47.5%, respectively). Only the methadone parent/metabolite ratio was significantly affected by benzodiazepines, with a 35% reduction with diazepam (11.8 vs. 7.7) (Dataset B).

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In conclusion, lower concentrations for certain opioids were found in deaths with increasing numbers of co-intoxicants and when a valid prescription was absent. Opioid metabolism is a complex process, affected by a number of factors. Some differential effects were present in parent and metabolite concentrations among the opioids studied with and without co-ingested benzodiazepines. Further studies are needed to characterize the factors that individually or when combined might affect opioid concentrations in unintentional overdose deaths.

Opioids, Benzodiazepines, Unintentional Overdoses

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