K11 Methadone to Metabolite Ratio in Cases of Fatal Overdose

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The goal of this presentation is to provide the attendees with information that is pertinent to the interpretation of methadone and methadone metabolite results in deaths that are due to methadone intoxication.

This presentation will impact the forensic community and/or humanity by demonstrating assisting forensic toxicologists and pathologists in evaluating methadone and methadone metabolite blood concentrations in cases of fatal methadone intoxication.

Identifying that a death has occurred due to accidental drug overdose requires consideration of a host of factors. The phenomenon of pharmacodynamic (cellular) tolerance is of particular significance in evaluating opioid blood concentrations in circumstances that suggest fatal overdose. Accordingly, opioid concentrations in those who have died from causes other than overdose are, for the most part, indistinguishable from those found in fatal overdose. With the recent increase in the prevalence of methadone in many areas, correctly identifying the extent to which methadone is causally related, whether as the sole agent in a fatal overdose, or its significance as a contributing factor in a multiple-drug overdose, is of increasing importance.

For many drugs, the concentration of parent drug relative to that of one or more metabolites provides an indication of the extent to which a drug was used during a period of time preceding death. With opioid drugs, awareness of their use prior to death is useful in assessing the degree to which the user may have developed cellular tolerance. A study published in 1988 by Hartman et al. (1) addressed the use of a propoxyphene metabolite as a means of evaluating chronic use, and hence, tolerance. Similarly, the purpose of this study is to assess the relationship between methadone and its principle metabolite, EDDP (2-ethylidene-1,5-dimethyl-3,3diphenylpyrrolidine), in cases of fatal overdose in which no alcohol or other drugs were detected. As an adjunct to case information about previous drug use, the role of the metabolite, EDDP, in relation to parent drug, methadone, is suggested. EDDP is formed by spontaneous cyclization following cytochrome P450-mediated *N*-demethylation of methadone.

Each case considered for inclusion in the study received a full autopsy performed at the West Virginia Office of the Chief Medical Examiner. Toxicological analysis was performed to determine the presence of volatiles in blood by direct injection GC-FID, drugs of abuse screening of blood and/or urine by enzyme-multiplied immunoassay technique (EMIT), and GC-MS screening of acidic/neutral and basic drugs in blood and/or basic drugs in urine. Positive drug screening results were confirmed and quantitated by GC-MS or LC-MS. Methadone and EDDP concentrations were determined in subclavian blood in each case by GC-MS using SKF525A as internal standard.

Data included in the study was limited to consecutive cases found to be "methadone only" drug overdoses which occurred in West Virginia between January of 2003 and July of 2005. During this time period, 21 deaths due to methadone intoxication were identified of which fourteen of the decedents were male and seven were female. Methadone concentration in subclavian blood averaged 665 ng/mL + 470 ng/mL and ranged from 98 ng/mL to 1846 ng/mL. Average EDDP concentration was 48.2 ng/mL + 39.3 ng/mL and ranged from 5 ng/mL to 150 ng/mL. The average ratio of blood methadone concentration to EDDP concentration was 16.1 + 5.8 with a range of 7.9 - 29.4. EDDP concentration was found to be correlated with that of methadone, $r^2 = 0.82$ ($p < 0.01$). A previous study has shown that methadone can be converted to EDDP as an analytical artifact due to an elevated gas chromatograph injector port temperature (2). The method of analysis also resulted in methadone conversion to EDDP, but was found to be less than 1.0% of the methadone concentration.

Consistent with previous reports, these data demonstrate that methadone blood concentrations in fatal overdose vary enormously. The ratio of methadone to EDDP may, however, provide additional information in establishing overdose in cases where overdose is supported by case information and no drugs other than methadone and its metabolite(s) are found. Methadone has a longer half-life than most other opioid drugs. For EDDP concentration to be useful as an indicator of chronic methadone use, it would need to be shown that it has a long half-life and that its concentration becomes elevated with chronic methadone use. At present, however, EDDP's half-life has not been clearly demonstrated. To more thoroughly affirm EDDP concentration or the methadone to EDDP ratio as potential indicators of tolerance, further study is needed of parent drug and EDDP concentrations in deaths in which the decedent was positive for methadone, but methadone was not a contributory factor in the death.

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References:

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Methadone, Opioid, Overdose

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