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Abstract

Determining the etiology or cause of an event in forensic cases often creates many theories. On piece of additional information which may be helpful in cases involving a drug or medication are concentrations or serum levels. Although many confounders can affect the interpretation of the drug level, it is imperative to also relate the data to the clinical scenario presented. Drug levels can be highly variable, depending on the time drawn, location from where the sample was obtained, and reference/references utilized in its interpretation. Postmortem drugs levels often do not reflect the blood levels before death. A drug level can be elevated exclusively because of postmortem distribution. This may result in a conclusion of a poisoning as the cause of death when in fact the death resulted from nonpharmacologic or nontoxicologic causes. Caution is advised from making any conclusions based solely on the drug level; rather an in-depth review of the clinical scenario, reference literature, and drug characteristics are required.

Keywords

drug, level, postmortem, toxicology, death

Introduction

The area of death investigation involves meticulous retrieval of information from either a physical location and/or often from data obtained from a subject. During the course of the analysis of a medication- or drug-related event, a routine part of the investigation centers on medication levels. Often these medication levels are drawn from the body during an autopsy. The serum levels needed for a case analysis from a laboratory can provide a screen for prescription medications, illicit substances, and environmental/occupational toxins. A common question in forensic pharmacology is whether the given toxicant caused or contributed to the death. Ideally, drug levels are most helpful if they are obtained immediately prior to and after a death. However, this is generally not the case. Autopsies and thus blood samples may not take place for days, weeks, or longer after the person died. The goal of this brief review is to discuss the variables associated with interpretation of postmortem drug (medication) levels and how to determine whether a drug plays a role in the etiology of an event in question.

Review of a Case File

The initial steps of an investigation require a careful review of the subject's case file. Prior to any interpretation of a drug level, there are several variables which need to be addressed. One such variable is the subject's medical history. The medical history can often provide vital information in regards to the patients past medical history, medication history (or evidence of prior exposure), and laboratory values which all need to be

integrated in order for a conclusion or opinion of the investigator to be formed.^{1,2}

The concept of a patient being naïve (or nontolerant) to medication exposure is often very helpful in determining initial reactions or side effects to a medication if they are exposed for the first time versus a subject that has a long history of medication exposure.¹ There are several types of information gathered during the investigation which can be grouped into either qualitative data or quantitative data. Qualitative data can provide information about exposure; however, no further details on the extent of exposure can be gathered.² In the case of quantitative data, a drug level from a site in the subject's body (ie, blood, organs, etc) can provide additional information with regard to the degree of exposure in many cases. In both scenario's, the investigator is cautioned about false-positive and false-negative results which may alter the perception and in some cases change the conclusion or opinion from a case review. The analytical procedure of choice for most substances is the gas-chromatography/mass spectrophotometry (GC/MS). The GC/MS has minimal changes for false positives in comparison to

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antibody-based tests. An additional piece of information that needs to be researched is the accepted range for these medications in the body. There are several references; however, using a standard text reference in this area would be of value.³⁻⁵ A toxicology reference provides factual information regarding a sub-therapeutic, therapeutic, or a toxic level; however, the value alone does not determine the etiology of an event. An investigator should consider specific autopsy findings that may indicate toxicity with a certain agent. For example, pulmonary edema is usually found in fatal overdoses with opiates.

Postmortem Considerations

The alterations and changes that occur to a medication after ingestion during life are grouped under pharmacokinetics. The concept of pharmacokinetics described the transformation of a drug via absorption, distribution, metabolism, and elimination that occurs during the process.^{1,6} Postmortem redistribution (PMR) is a term used to describe the changes that may occur after death in the human body and relates it to alterations in chemistry and pharmacology which need to be considered. Changes that occur in drug levels due to redistribution are also termed necrokinetics. The concept of necrokinetics is critical when interpreting the postmortem drug level. PMR can be divided into categories: physiologic changes in the body after death (macro level and cellular level) and drug characteristics.^{1,2} The quest for research into the drug changes which occur during PMR are inherently difficult to construct and incomplete for obvious reasons; therefore a fair amount of data is available from animal models as well.

Physiologic Changes in the Body After Death

At a cellular level, there are several changes to incorporate into an investigation. The main variables affected after death are cell membrane, respiration, synthesis of proteins, and preservation of deoxyribonucleic acid (DNA). All of these are affected after death and need to be considered. For example, cell death can result in a release of its cellular contents and/or create an environment of acidosis secondary to anaerobic metabolism that occurs. In addition, blood potassium (K) levels are increased postmortem secondary to cessation of the Na/K ATPase pump function.⁷ Drugs also have the capability to diffuse from organs/tissues in the body and back into circulation as this process is passive. In addition, body decomposition or putrefaction can create an environment in which bacteria can either facilitate further metabolism of the drug or in some instances substances can be produced during putrefaction. For example, alcohol can be produced secondary to the process of putrefaction which begins shortly after the time of death.⁸ In addition, the main substrate for ethanol production is glucose; therefore after death the liver, lungs, and heart can be sites where it is generated and detected. The major sites of drug deposition are lungs, heart, liver, and gastrointestinal tract (GI). Depending on the drug characteristics, medications are able to facilitate movement from these areas and translate into

either lower or higher than normal blood levels.⁹ For example, alcohol is well known to diffuse from the GI tract into circulation after death.¹⁰ In addition, certain organs facilitate the process easily secondary to enriched blood supply to the area, vascular access to the body, and thickness of the membrane to allow diffusion as is the case for the lungs. The liver appears more complicated as the drug can diffuse via hepatic circulation and/or directly into organs which are adjacent. The heart is also more complex, in the respect that drugs may concentrate into the organ initially while a subject is alive; however after death the right/left chambers can serve as a sampling site post-mortem.¹¹⁻¹³

Drug Characteristics

The drug characteristics that are involved in PMR are the following: absorption, distribution, metabolism, and elimination. Absorption can be affected by the integrity of the cell membrane and the pH of the medium. Movement of the drug can also be affected by the lipophilic solubility and the ionic state (ie, pKa) of the drug as well. Drugs that possess lipophilic properties are able to concentrate in major organs (ie, heart, lungs, and liver).^{1,6} In addition, after death the cellular medium becomes more aqueous and acidic, therefore movement of basic drugs becomes more likely as well. Distribution of drugs can also be altered after death.^{12,13} In general, drugs which are more lipophilic will tend to have further redistribution after death and can translate into increased movement from tissues/organs into circulation where these are measured.² The volume of distribution (Vd) refers to the total volume into which the total amount of drug would be distributed in order to reach the plasma. According to several experts, a Vd of greater than 3 to 4 L/kg can be indicative of PMR changes and increasing serum concentration after death.^{2,14} However, this is not an absolute rule. Drugs which are highly protein bound generally will not have a high or extensive Vd; however drugs which are not heavily bound to plasma proteins are able to undergo PMR changes. An example, morphine is a drug that undergoes extensive metabolism and its glucuronide by-products can be detected after death. Additional examples are included in Table 1.¹⁵ Drugs possess certain characteristics that would make them more likely to stay within the plasma or even decrease after death. Characteristics that are notable are polar compounds and medications with a low Vd (eg, valproic acid, antibiotics, and furosemide).^{1,16} Metabolism is also affected during PMR. Metabolism can persist for several hours after death has occurred and can include the breakdown of drug into metabolites and by-products. The importance of obtaining a drug/metabolite level would be helpful in the investigation in order to determine the true effect of PMR on the metabolism process. Elimination of drug occurs mainly via the hepatic and renal routes. Both processes are affected shortly after death and can result in accumulation of drug/metabolite/metabolites which may later be detected via laboratory analysis. The main factors regarding drug characteristics which are known to affect PMR include lipophilic nature, pKa, and Vd.^{16,17}

Table 1. Drugs and Toxins Which May Undergo PMR^{2,4,16}

Alprazolam
Amitriptyline
Amphetamine
Cocaine
Dextromethorphan
Diazepam
Flecainide
Gammahydroxybutarate
Haloperidol
Ketamine
Lidocaine
Morphine
Nicotine
Phencyclidine
Propafenone
Remifentanyl
Sufentanil
Venlafaxine
Zolpidem

Abbreviation: PMR, postmortem redistribution.

Analysis of Drug Level Information

An investigator needs to have several concepts at the base of their practice when beginning the process of the analysis of all the information and data available. One key factor is to review the clinical scenario presented, then begin using the subject's information to integrate the past medical history, medication profile (recent and past), and laboratory information (where applicable). These series of steps can provide guidance in order to formulate the appropriate conclusion or opinion. One step that would be helpful in the drug level analysis would be the central to peripheral blood compartment ratio (C/P). The C/P ratios are generally the highest for basic compounds with a large Vd.^{2,18} A caution about C/P ratio is that there is active research as to whether or not these are able to be correlated to therapeutic, toxic, or fatal drugs levels; therefore the interpretation and true utility of these is still debated. An additional factor that needs to be determined is the timing and location of the sample of the drug level postmortem.^{12,19,20} The time of the autopsy will not reflect the drug level at the time of death. Autopsies may be performed after hours of death, days, weeks, or months. The time length between death and autopsy can translate into changes in concentrations of a drug and/or its metabolite/metabolites as well. Generally, the drug is less likely to be altered in the peripheral compartment immediately after death; however, the central compartment (blood from the heart) can reflect a higher drug level secondary to diffusion and translocation of the drug from other compartments (ie, lungs) especially those with a high Vd.^{19,20} In addition, there are inherent challenges with postmortem drug levels. Newly introduced drugs by the Food and Drug Administration (FDA) often may not have therapeutic-defined serum reference levels and/or a standard assay to measure them. In clinical practice, blood samples (including drug levels) are typically obtained from a peripheral vein in the arm. During an

autopsy, a blood sample may be obtained from the femoral artery or the heart chamber.

Another technique when reviewing postmortem drug levels is to review the subject's medical records that note the patient's condition before death. Did the subject exhibit classical signs and symptoms of the toxicity of the suspected agent. For example, a person overdosing on bupropion would have convulsions. When the suspect is treated in a hospital, via ambulance, or other clinical situation just prior to death the relevant records should be reviewed as part of the forensic investigation. Unfortunately, a common scenario is that the decedent is found in the home after an apparent sudden death.

Summary

An investigator has several important concepts to incorporate during the analysis of a postmortem drug level. The analysis of the subject case involving the integration of past medical history, medication history (past and current), and laboratory values is vital in determining a plausible scenario. The information recorded above will allow the investigator to proceed with the next steps in determining time and the location in the body that the postmortem drug levels were obtained. As autopsies may not be performed the same day as a subject's death, PMR may have a significant role on drug levels, depending on the drug/drugs in question. Finally, the investigator needs to concentrate on several drug properties that can alter the drug level postmortem and these include, but are not limited to, the lipophilic nature, pKa, and Vd of the drug.^{14,16} A careful analysis of the subject's case, autopsy report, and review of the drug/drugs characteristics allows the investigator to form a more sustainable conclusion or opinion for a forensic case involving a postmortem drug level.¹⁹

Declaration of Conflicting Interests

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