

Forensic Pharmacokinetics: A New Dimension for Drug Related Medico Legal Cases

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Abstract

The incident of drug related medico legal cases are increasing day by day. In Forensic Medicine there is a need of frequent requirement of estimation of dose size administered or ingested by deceased, based on either postmortem blood level or concentration of drug in urine. In an ideal situation creatinine clearance should be evaluated than it is corrected according to age, sex and body surface area. Postmortem changes begin at cellular level with the onset of ischaemia. Depending on duration of ischaemia structure and function of organs and tissue gradually deteriorate which influence the distribution of drugs in the body fluids and tissues. For estimation of drug concentration of deceased, there is need to consider the postmortem redistribution phenomenon. Deceased drug concentration may not reflect the actual concentration at the time of death, similarly there is possibility that miss calculation from deceased blood level if it is not judiciously used to simulate the dose versus toxicity relationship. In this article authors have emphasis on various aspect of co-relation of drugs level following death and different factors that influence while predicting actual drug concentration for medico legal drugs related cases.

Keywords: Drug concentration; Postmortem; Legal implication

Introduction

The incidence of drug related medico legal cases are increasing day by day, with the advent of newer drugs on an almost daily basis, the number of medico legal cases due to complication (accidental or deliberate) of these drugs are increasing at an alarming rate. Not only therapeutic agents, the cases of poisoning from know toxicological agents like organophosphorous compounds, aluminium phosphide etc. are increasing with each passing day. In such scienerio, the toxicologist has to determine the amount of the suspected poison in the dead body from the samples preserved during autopsy. But, are the results that we get from such samples accurate? Can these results be extrapolated to the living to get the amount of drug present at the time of death? Does the time passed since death has any bearing on these value? What is the correlation we get in blood and various organ? These are many such question need to be answered before we can use the toxicological analysis for legal evidence on the basis of these results [1,3].

All drugs have the potential to be misused, whether legally prescribed by a doctor, purchased over-the-counter at the local drug store, or bought illegally on the street. Taken in combination with other drugs or with alcohol, even drugs normally considered safe can cause death or serious long term consequences. Accidental drug overdose may be the result of misuse of prescription medicines or commonly used medications like pain relievers and cold remedies. Symptoms differ depending on the drug taken.

While many victims of drug overdose recover without long term effects, there can be serious consequences. Some drug overdoses cause the failure of major organs like the kidneys or liver, or failure of whole systems like the respiratory or circulatory systems. Patients who survive drug overdose may need kidney dialysis, kidney or liver transplant, or ongoing care as a result of heart failure, stroke, or coma. Death can occur in almost any drug overdose situation, particularly if treatment is not started immediately.

Drugs are generally classified as either

Prescription: These require a doctor's authority to purchase them.

Some common examples are; 'Valium'(diazepam), 'Morphine', and 'Benzodiazepines' (sleeping tablets) etc.

Non-prescription: Are drugs which may be purchased without prescription. They consist of headache compounds, cough elixirs, and similar mild medications, and can be purchased at virtually any chemist or retail outlet. Common examples are; 'Panadol', 'Aspro', 'Vick's Cough Syrup', alcohol, and nicotine (cigarettes).

Illicit: Are drugs that are imported, grown or manufactured illegally. All illicit drugs are dangerous and usually imply a degree of dependence, or in some cases, addiction. Examples are; heroin, cocaine, amphetamines, 'ecstasy', marijuana, meth and LSD.

In a study conducted in Utah between 1991 to 2003, it has been observed that there is tremendous increase in number of death caused by use of non-illicit drug poisoning, and most of them was unintentional in nature. While in 1991, only 50 people died because of use of non-illicit drug, the number rose to more than 250 by 2001 [29].

Processes by which the movement of drugs and other chemical poisons between tissues, organs and body fluids takes place after death is known as post mortem drug distribution [1]. This phenomenon is well recognized and was first reported 25 years ago [2].

Cases of suspected poisoning, either homicidal or suicidal, the role of drugs in "marginally toxic" cases, such as vehicle accidents, and also potential toxicological cases of euthanasia or medical negligence might

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rely upon the toxicological analysis of blood samples and in these situations one has to consider the role of postmortem drug distribution for analysis of results of postmortem blood samples [3].

The timing, method of collection, and source of sample might influence the interpretation of toxicological analysis. The process of postmortem distribution results in the migration of drugs between blood and tissues, the rate and extent of which varies according to several factors, including the nature of drug and time interval between death and post mortem specimen collection.

The major organs constitute potential drug pools, and the gastrointestinal tract might contain considerable quantities of unabsorbed drug, and thus central blood is subject to redistribution from these local organs. Peripheral blood, such as femoral blood, is subject to redistribution influence only from local tissues-muscle and fat.

So, redistribution into central vessel is greater than that of peripheral vessels. For these reasons, the blood specimen of choice for toxicological analysis after death is a femoral venous sample, ideally collected from a ligated vessel [4,5].

Often, toxicologists are requested to estimate the amount of drug present at the time of death. This assumes that the drug concentration found at the time of post mortem is a reliable estimate of that present at the time of death. There is lack of evidence that such an extrapolation is possible, in only a few cases reported, antemortem blood concentration are available for comparison with values from variety of sites at post mortem examination [6].

In cases where intervals between antemortem sampling and death was known, and an estimate of the plasma concentration at the time of death was calculated using the following equation to account for the decline in drug concentration as a result of ongoing metabolism and elimination during life-

$$\ln N_t = \ln N_0 - Tn^2[T/t_{1/2}]$$

N_t =calculated plasma drug concentration at time of death; N_0 =plasma drug concentration at time of sampling; T =time interval between sampling and death; $T_{1/2}$ =elimination half life of drug in plasma [7,8]. Drugs with high central to peripheral ratio also tend to have a high postmortem to antemortem ratio. Overestimation of the ante mortem drug concentration results in an artificially low postmortem to antemortem ratio. It can be dangerous to attempt to relate a drug concentration found at postmortem examination to the antemortem circulating concentration or the antemortem dose received. It is not possible to form a general rule regarding the differences between the antemortem and postmortem drug measurements as variation seen depends on the nature of drug.

Variables affecting central to peripheral ratio: Increase in interval between death and postmortem examination affect site specific postmortem drug concentration to a great extent, and hence the central to peripheral ratio calculated [9]. It is likely that this interval will also affect the postmortem to antemortem ratio calculated for the drugs, although drug concentration in the femoral vein after death appear to be relatively stable with time, again making any extrapolation using these ratios unsafe [10,11].

To determine whether the drug concentration found at post mortem examination should be attributed to either therapeutic ingestion or overdose is very difficult because of the influences of post mortem changes.

Use of postmortem to antemortem ratios, or back extrapolation from a postmortem concentration, is not recommended. For certain drugs, it may be more appropriate to consider the parent to metabolite ratio. It has been shown consistently for several drugs (e.g., tricyclic antidepressants) that a high ratio is indicative of acute administration, as seen in overdose, because often *in vivo* metabolism is saturated or incomplete and circulating concentration of the parent compound remains high [12,13,14].

Postmortem to antemortem blood drug concentration ratios for both heart blood and blood from vena cava and also the lung to antemortem blood drug concentration ratio were closely related to the apparent volume of distribution for the drugs. Accordingly, an apparent volume of distribution of more than 3-4 L/kg is a good predictor that a drug is liable to undergo post mortem redistribution with significant increments in blood levels. Drugs like tricyclic antidepressants; barbiturate, opiates and others show postmortem concentration increases in humans [15]. On the other hand, there are substances that redistribute insignificantly post mortem, as acetaminophen and zopiclone [16].

After death, several mechanisms can give rise to artificially increased blood drug concentration. A drug may be released postmortem from tissues with high drug concentration and redistribute by means of diffusion and convection of blood and other fluids in the body. The lungs have been experimentally verified as a source of post mortem drug release to the blood [17] but also liver, myocardium, endothelium and kidney are possible sources. Drug distribute from unabsorbed from stomach, drug depots to anatomically adjacent tissues like the left lobe of the liver, left lower lobe of the lung and eventually myocardium and blood in central compartments [18,19,20]. Agonal or postmortem reflux of drug-rich material from the stomach into airways followed by release to the blood can give rise to falsely elevated drug concentration in heart blood and other central tissues [21].

Postmortem to antemortem blood drug concentration ratios for acidic/neutral drugs as Phenobarbital, acetaminophen or carbamazepine were close to 1.0. For the basic drugs codeine, amphetamine, verapamil, and trimeprazine, there were significantly elevated postmortem to antemortem blood drug concentration ratios [22].

Calculation of blood alcohol concentration for forensic purposes are based on several simplified assumption like linear pharmacokinetics of ethanol, constant value of ethanol elimination, constant rate of alcohol absorption and constant time to achieve peak blood levels, which is by convention depends only on type of beverage and quantity of food consumed. These simplified and idealized assumptions significantly restrict possibility of back extrapolations of blood alcohol concentration from the observed values and calculations based on them exclude the absorption phase of blood alcohol curve. Although many factors may alter the concentration of alcohol present in autopsy specimen, postmortem synthesis of alcohol receives most attention. The microorganisms producing ethanol post mortem can be inhibited by adding a preservative and storing the sample under refrigeration [23].

There did not seem to be any relationship between the postmortem changes and pharmacological parameters such as acid dissociation constant (pKa), molecular size, plasma protein binding or lipophilicity. The basic lipophilic drugs may interact through inhibition of accumulation in the isolated perfused lung depending on their lipid solubility [24].

Lungs function as a reservoir for antidepressants [25]. Addition of a second antidepressant cause release of the first drug in volunteers, with an increased risk of toxicity. It has been established that cationic amphiphilic drugs accumulate in tissues by two major mechanisms, namely non covalent binding to membrane phospholipids and ion trapping within acidic cellular compartments like lysosomes [26]. The tissue to blood drug concentration ratio of the lung was found to be predictive of the postmortem drug level increase observed in heart blood. This is in agreement with a previous study in rats showing that removal of the lungs significantly reduced the postmortem drug level increase observed in heart blood for amitriptyline.

The apparent volume of distribution is defined as the amount of drug in the body divided by plasma or blood concentration at distribution equilibrium. The highly significant co-variation between the postmortem drug level increase and the volume of distribution shows that the latter is a very useful measure for assessing drugs for the possibility of postmortem redistribution. It also correlates the fact that the apparent volume of distribution of a drug also expresses the average tissue to blood concentration ratio. It is a measure for the concentration gradient between tissue and blood. Fick's law of diffusion states that the rate of diffusion of a substance is proportional to the concentration gradient across the diffusion barrier. Consequently, the apparent volume of distribution is a logical measure for the liability of a drug to redistribute from tissues to blood after death.

Recommendations

Procedure for ideal blood sampling in postmortem cases: A standard protocol has to be developed for toxicological samples collection at post mortem examination. Chosen method must be easily incorporated into routine post mortem practice. Blood for quantitative analysis (≥ 5 ml) should be taken from two distinct peripheral sites, preferably left and right femoral veins. Femoral blood can be taken by cutting the external iliac vein proximal to inguinal ligament, and milking the distal cut end into the specimen tube. Early ligation of this vessel is recommended to avoid mixing with more central blood during evisceration. An additional larger specimen of blood (≥ 20 ml) for qualitative screening can be collected from a convenient large vessel [27,28].

Following death there can be rapid changes in cellular biochemistry as autolysis proceeds, and drugs and other poisons may be released from their binding sites in tissues and major organs, also unabsorbed drugs may diffuse from the stomach. Special care should always be taken in the selection of blood and tissues sampling sites, the method of collection of samples, and the labeling of sample containers.

In case of liver and lung, recommended sites are right lobe of liver and apex of the lung. The concentration of drug found in post mortem blood specimens, even those taken from peripheral sites, will often much higher than the perimortem plasma drug concentration particularly if several days have been elapsed between death and postmortem. It is not scientifically valid to compare the reported postmortem drug concentration of a drug with literature values of plasma drug concentrations in cases of drug over dosages. Similarly the practice of calculating the dose of ingested drug or poison from the product of the postmortem blood drug concentration [C] and the reported volume of distribution [Vd] {Dose = C x Vd} is not recommended. Interpretation of findings can present a problem where there is little background information concerning the case, or where specimen collection has been inadequate. Interpretation of findings can

also be difficult in drug abusers where the likely degree of "tolerance" to a drug is unclear because of inadequate history. The recent history, age and state of health are also important factors to be taken into account during interpretation. Presently there are very few literature available on postmortem changes of drugs and there is need for future extensive research to address various issue on drug related medicolegal cases to find out the better correlation of drug level with postmortem changes.

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