Brain Tissue: A Viable Postmortem Toxicological Specimen

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Introduction

The determination of cause and manner of death relies upon scene investigation, medical history, autopsy examination and toxicological analyses. Postmortem specimens that are subjected to toxicological examinations range from bodily fluids to tissues, generally focusing on blood and urine. The interpretive challenges with urine results are that a positive finding only reflects recent exposure, since the bladder is pharmacologically outside the body. Postmortem blood concentrations may not necessarily reflect the drug concentration at the time of death; as drug concentrations may change as a result of body storage conditions, time and site of blood sampling. Although interpretation is possible, it must proceed with caution. Analysis of blood from different anatomical sites and tissue samples may assist in the interpretation of the postmortem results.

In many postmortem cases, there is little to no blood for quantitative drug analyses, traumatic injury may lead to significant blood loss or contamination from ruptured stomach contents. The protected and isolated position of the brain may eliminate the challenges of postmortem redistribution (PMR) and delay or attenuate residual enzymatic activity on certain substrates artifically altering their concentration. Brain tissue is more immune to decomposition allowing for the detection and quantitation in this sample when compared with centrally located organs (e.g., liver) and cavity fluid. Thus, brain tissue has some advantages over other specimens collected at autopsy.

Although Baselt (1) has some brain data in individual monographs, overall there is a paucity of data as to the quantitative distribution of drugs into brain tissue. The limited amount of data comparing brain concentrations to paired blood concentrations makes the interpretation difficult when brain tissue is the only viable specimen for testing. It is recognized that a direct quantitative relationship cannot be achieved relating blood concentrations to tissue concentrations. This is due to several factors, the measured drug concentration at the time of death may not reflect complete distribution, that is, acute overdose and/or PMR may skew the relationship. Nonetheless, positive trends or correlations are observed and may assist in the interpretation of the toxicological results, where brain tissue may be the only viable sample for analyses.

Results

Table I is a compilation of the results gleaned from the RFSC toxicology case files. The concentrations listed in Table I reflect mean concentrations, with the ranges reflecting the variation of the ratio over the sample size evaluated.

Some general trends in drugs belonging to the same structural or pharmacological class are observed in Table I data. Opioids generally tended to have a heart blood concentration that is about half of the brain concentration. Cacaethylene and cocaine, which differ only in a methyl group, have very close heart blood (HB)/brain (Br) values (0.51 and 0.44, respectively). The first-generation H1 antagonists chlorpheniramine, promethazine and diphenhydramine have HB/Br values of 0.11, 0.29 and 0.50, respectively. Orphenadrine is classified as an ethanolamine antihistamine, closely related to diphenhydramine, and has an HB/Br of 0.28. Doxylamine, another ethanolamine antihistamine, has an HB/Br of 0.42. Although the sample size is small, there appears to be some overlap in the ratios, which would not be unexpected. Benzoylecgonine (HB/Br 2.27) is a carboxylic acid, and does not readily cross the blood–brain barrier. A lower concentration in the brain than in the blood would be expected. Upon comparison of the mean blood/brain ratio to the median ratio, it was found that they were in general agreement.

Hiberg et al. (2) found that with a high volume of distribution, high PMR is expected. This would result in a low HB/Br. This can be seen in Table I with several of the drugs that have a high Vd and also have the expected low HB/Br, such as chlorpheniramine (Vd 3–6 L/kg, HB/Br 0.11), dextromethorphan (Vd 3.0 L/kg, HB/Br 0.23), meperidine (Vd 3.7–4.2 L/kg, HB/Br 0.25), meperidine (Vd 3.7–4.2 L/kg, HB/Br 0.25),...
blood samples generally have lower concentrations than central samples due to less PMR (3), thus more closely approximates the ante-mortem concentration. However, femoral blood samples are not totally immune to the effects of PMR.

Brain tissue has many potential advantages for postmortem toxicological analysis. It is anatomically sequestered, less putrefaction occurs, and there is lower metabolic activity (4–6). Kugelberg et al. (7) found variation in brain levels to be less than femoral blood. The brain undergoes less PMR (8) and brain concentration has been found to be more stable over time when compared with other sample sites (4).

Several studies have found that drug concentrations are homogenous throughout the brain. Wille et al. (5) determined distribution of antidepressants throughout the brain to be homogeneous. Kornhuber et al. (9) found that amantadine concentrations appear to be homogeneously distributed throughout the human brain. Kalasinsky et al. (10) observed only slight regional differences in brain tissue for cocaine and its metabolites (benzoylcegonine, ecgonine methylester, norcocaine and cocaethylene). The same observation was made by their group for methamphetamine and amphetamine (11). Scheyer et al. (12) noted in two surgical patients, who were undergoing phenytoin therapy, that there was not observable differences in drug concentration between various sites of the brain.

However, other authors have found some evidence contrary to this. In a study by Stimpfl and Reichel (6), overall data indicated that the distribution of morphine, dihydrocodeine and benzoylcegonine was homogenous in the medulla oblongata and cerebellum. This same study also showed, however, that when the two regions were compared in individual cases, the cerebellum. This same study also showed, however, that when the two regions were compared in individual cases, the cerebellum. This same study also showed, however, that when the two regions were compared in individual cases, the cerebellum. This same study also showed, however, that when the two regions were compared in individual cases, the cerebellum. This same study also showed, however, that when the two regions were compared in individual cases, the cerebellum. This same study also showed, however, that when the two regions were compared in individual cases, the cerebellum.
white and gray matter of the brain. However, they observed that carbamazepine concentrations were slightly higher in the white matter when compared with the gray matter and with phenytoin they observed it was ≈1.4 times higher in the white matter when compared with the gray matter of the brain.

Morselli et al. (16) observed that there was a differential distribution of carbamazepine in brain tissue. They found that carbamazepine was higher in the parieto-occipital region when compared with the temporal region of the human brain.

Alprazolam and zolpidem have relatively low volumes of distribution and are less likely to undergo PMR when compared with weakly basic drugs with higher volumes of distribution. The blood to brain ratio of these two compounds are close to unity. This is consistent with what has been observed by other weakly acidic/neutral drugs with low volumes of distribution, such as carbamazepine with a blood–brain ratio of 0.91 (16), phenobarbital with a blood–brain of 1.09 (14) and phenytoin with the greatest deviation from unity with a blood–brain ratio of 0.67 (14). Drugs with a large volume of distribution (>3–4 L/kg) are generally believed to be more apt to undergo PMR (2, 3). The blood–brain ratio for these drugs tends to be significantly lower, with most <0.5. There are two notable exceptions, benzoylcegonine and morphine. However, given their polar nature and limited ability to cross the blood–brain barrier, this is not unexpected. Tetrahydrocannabinol (THC) also has a high ratio and it mostly likely due to sequesteration in other deep lipophilic depots of the body.

The data presented in this study will provide another tool for the toxicologist and pathologist for the interpretation of postmortem toxicological results. The study groups together a large number of variables between the cases and circumstances. Although there are a wide range of cases and circumstances. Although there are a wide range of variables between the cases and circumstances. Although there are a wide range of drug concentrations, positive correlations were observed and will provide objective data to evaluate a brain drug concentration.

References