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Identification of a *postmortem* redistribution factor (*F*) for forensic toxicology

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Abstract

Background: *Postmortem* redistribution (PMR) refers to the changes that may occur in drug concentrations after death. Consequently, *postmortem* concentrations in blood may not always replicate the *antemortem* drug levels. Literature supports the model describing drugs with a liver (L) concentration to peripheral blood (P) concentration ratio less than 5 (L/kg) being prone to little or no PMR. Conversely, drugs with a L/P ratio greater than 20 to 30 (L/kg) have propensity for substantial PMR.

Findings: Expanding upon this prior work, the current paper presents the concept of a *postmortem* redistribution factor (*F*) for a drug, which characterizes the direct relationship between *postmortem* peripheral blood and the corresponding *antemortem* whole blood concentration.

Conclusions: Development of the concept of a "*postmortem* redistribution factor" will provide a more definitive and authoritative drug ranking, and possibly, numerical interpretation of PMR for forensic toxicologists.

Keywords: *Postmortem* redistribution factor; Peripheral blood; Liver; *Antemortem*; Concentration; Ratio

Findings

Introduction

A potentially significant issue complicating interpretation of *postmortem* drug concentrations results from the phenomenon referred to as *postmortem* redistribution (PMR). *Postmortem* drug concentrations in the blood may not always straightforwardly parallel *antemortem* drug concentrations in the blood due to the movement of the drugs after death. Accordingly, some authors have argued a cautious approach in interpreting *postmortem* concentrations, and others have taken a far more pessimistic and even cynical perspective. The mechanisms involved in PMR are both complicated and poorly understood. However, *postmortem* drug concentrations in the blood may follow some commonly accepted trends that aid with interpretation. Generally, the characteristics of the drug itself can be used to predict if a drug is subject to PMR. Substantial changes in blood drug concentrations are predicted for basic, lipophilic drugs with a high volume of distribution (>3 L/kg) (Prouty & Anderson 1990). When PMR occurs, blood specimens drawn from the central body cavity and heart generally exhibit higher drug concentrations *postmortem* than specimens drawn from peripheral areas, most commonly the femoral region. Diffusion of drugs from organ tissues into the blood may explain the observed phenomenon.

Previous attempts to assess and account for PMR have utilized *postmortem* blood specimens collected from at least two areas of the body at autopsy, a peripheral area and a central area (often the heart), so that a comparison could be made. The resulting *postmortem* blood ratio was considered to reflect a drug's potential for PMR (Prouty & Anderson 1990; Dalpe-Scott et al. 1995). Recent work, however, has described ambiguities with this approach (McIntyre et al. 2012).

The collection, analysis, and comparison of *antemortem* blood specimens are obviously helpful in assisting with the interpretation of *postmortem* blood drug concentrations, but relevant specimens are only rarely available. In a set of case studies of six drugs, concentrations in the *postmortem* femoral blood specimens exceeded the *antemortem* concentrations in five of the drugs studied, suggesting that even peripheral blood exhibited redistribution (Cook et al. 2000). The potential for redistribution of other drugs in *postmortem* peripheral blood has also been documented (Gerostamoulos et al. 2012).

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The liver (L) to peripheral blood (P) ratio has been proposed as a more dependable marker for PMR, with ratios less than 5 (L/kg) indicating little to no propensity towards PMR, and ratios exceeding 20 to 30 (L/kg) indicative of a propensity for substantial PMR (McIntyre et al. 2012). A number of reports elaborating on, and supporting, this model have now been published (McIntyre & Mallett 2012; McIntyre & Meyer Escott 2012; McIntyre & Anderson 2012; McIntyre et al. 2013a; McIntyre et al. 2013b). Furthermore, a direct correlation between the *postmortem* peripheral blood and corresponding *antemortem* concentration - by consideration of the L/P ratio - has been expressed (McIntyre et al. 2013c). The report, describing methamphetamine cases, found that the *postmortem* peripheral blood concentrations were approximately 1.5 times higher than the corresponding concentrations attained in whole blood specimens collected before death. Given that the L/P ratios for methamphetamine had been confirmed to be approximately 6 (L/kg), it was then projected that drugs exhibiting L/P ratios between 5 and 10 (L/kg) would theoretically yield *postmortem* peripheral blood concentrations up to twice the corresponding *antemortem* concentrations - a measure of PMR potential. It was further hypothesized that L/P ratios ranging from 10 to 20 (L/kg) would demonstrate greater potential for PMR with *postmortem* peripheral blood concentrations 2 to 3 times that of the corresponding *antemortem* levels and consequently even higher L/P ratios indicative of even greater potential for PMR.

The current document sets out to expound upon this L/P model and its resultant implications by proposing the concept of a *postmortem* redistribution factor (F) for a drug. The *postmortem* redistribution factor has been defined as a factor that characterizes the direct relationship between a drug's *postmortem* peripheral blood and the corresponding *antemortem* (AM) whole blood concentration.

Hypothesis

Equation 1 presents the proposed relationship between the *antemortem* whole blood concentration of a compound and the corresponding *postmortem* peripheral blood concentration:

$$\mathbf{AM}=\mathbf{P}/\boldsymbol{F} \tag{1}$$

where AM = *antemortem* whole blood concentration, P = *postmortem* peripheral blood concentration, and F = *postmortem* redistribution factor.

Rearrangement of Equation 1 gives

$$\boldsymbol{F}=\mathbf{P}/\mathbf{AM} \tag{2}$$

Thus, an example of an experimental (or actual) F could be determined for a drug where both the *postmortem* peripheral blood and *antemortem* whole blood drug concentrations have been determined in the same individual (assuming an insignificant delay between the collection of the *antemortem* blood and the time of death).

Discussion

Considering the methamphetamine data (McIntyre et al. 2013c), an experimental (actual) F for methamphetamine of 1.5 is predicted - *postmortem* peripheral blood concentrations being 1.5 times (on average) greater than the corresponding *antemortem* concentrations.

A related approach to assess potential for PMR has also recently been described (Launiainen & Ojanpera 2013). This study presented data for 129 drugs comparing *postmortem* femoral blood concentrations to therapeutic plasma concentrations to describe drugs' propensity for PMR. This study analyzed a large number of cases where median *postmortem* drug concentrations were compared with estimations of the therapeutic concentrations. These authors projected a similar ratio for methamphetamine of 1.8. Although these data represent a practical attempt to describe PMR, it is conceivable that the determination of an F value from analytically determined *postmortem* data (such as the unique drug L/P ratio) may well produce more consistently accurate estimates.

The principal goal of these endeavors was to attempt to develop a ranking of drugs and indicate their propensity for and, subsequently, their potential extent of PMR. Until now, most efforts in interpretation have simply described PMR by an aphorism, ranging from 'the drug has not been found to exhibit PMR' to 'the drug is subject to PMR.' Such descriptions have never been particularly useful in the interpretation of *postmortem* drug concentrations, especially in relation to deducing what the drug concentration may have been at the time of death. The development of the concept of a systematically based *postmortem* redistribution factor will provide a more definitive and authoritative ranking and possibly numerical interpretation of PMR.

Competing interests
The author declares that there are no competing interests.

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