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Review

Postmortem drug concentration intervals for the non-intoxicated state – A review

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ABSTRACT

In postmortem toxicology, it is important to know what the usual drug level is in blood under ordinary therapy to make correct interpretations with regard to the possible occurrence of poisoning. A commonly used source is The International Association of Forensic Toxicologists (TIAFT) list of drug concentrations providing therapeutic drug levels, usually measured in serum. In this article, published postmortem-derived blood drug reference concentration intervals were related to therapeutic serum levels of drugs from the TIAFT list to assess agreement or discrepancies with focus on the importance of postmortem redistribution. The ratio between the upper limits was evaluated. This ratio ranged from 0.13 to 11.3 for 57 compounds with a median value of 1.5. For about a third of the compounds the ratio exceeded three. There was a tendency that for highly water-soluble drugs with a low propensity for redistribution, the ratio was generally low. For example, for pentobarbital, carisoprodol, meprobamate, carbamazepine, phenazone and theophylline, the ratio ranged from 0.14 to 1.1 with a median of 0.4. For the 15 antidepressants considered, on the other hand, the ratio was relatively high, ranging from 0.6 to 4.7 (median 2.4). For antipsychotics, the ratio ranged from 0.2 to 11.3 with a median of 1.4. In conclusion, there were generally wide discrepancies between serum-based intervals as presented in the TIAFT list and published postmortem blood-based drug reference intervals. More focus on postmortem-derived intervals is encouraged, so that those that have been estimated are cited in reference publications and so that further intervals are estimated. Ultimately, a reliable database of postmortem blood-based drug reference intervals for use by the forensic community is desirable.

1. Introduction

To interpret postmortem drug concentrations in blood or tissues it is important to have knowledge of the concentrations usually observed under therapeutic conditions. Commonly, plasma or serum concentrations observed *in vivo* under therapeutic circumstances or in pharmacokinetic studies are used as reference concentrations. For example, the concentrations referring to the therapeutic situation displayed in The International Association of Forensic Toxicologists (TIAFT) listing of reference blood levels[1] are serum concentrations, and in compilations of drug concentrations for forensic use, the references to the therapeutic situation usually are based on *in vivo* studies, see, for example, the handbook by Baselt and the compilation by Schulz and Schmoldt.[2,3] By referring to *in vivo* conditions, the phenomenon of postmortem redistribution is not taken into account.[4,5] In addition, a possible discrepancy between plasma/serum and full blood concentrations is not considered.[6] In a few compilations and some studies on specific drugs, reference is provided to postmortem drug concentrations for the therapeutic situation, or more precisely, the presumed non-intoxicated state.[7–17] Druid and Holmgren present the most comprehensive compilation with 83 drugs and/or metabolites from various drug classes. Reis et al. present a compilation of 15 antidepressants with metabolites. The other studies concern single compounds mostly of the psychoactive type. Thus, postmortem-derived reference intervals are available only for a limited number of compounds. This may appear somewhat surprising, since there has been so much focus on the phenomenon of postmortem redistribution over the years.[4,5,18] Much attention has been given to the group of antidepressants, where measurements before and after death, supplemented by experimental studies, have pointed in the direction that postmortem levels exceed antemortem levels by several folds.[5,18,19] The differences are most pronounced in the central vessels and heart, and much focus has been directed on the heart/femoral vein concentration ratio.[20] Although this ratio is of interest as an indicator of the degree of postmortem redistribution, in the postmortem situation it is the actual intervals observed in a peripheral vein corresponding to the intoxicated and non-intoxicated situations that are of primary relevance when considering cases. In this overview, focus is on the

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relations between postmortem and *in vivo* concentrations for the presumed non-intoxicated situation.

2. Factors of importance for interpreting postmortem measurements in relation to published *in vivo* serum levels for the presumed non-intoxicated situation

2.1. Analytical methodology

Variation in analytical technology may result in differences between actual measurements and reports in the literature. Differences are expected over time related to the development of more sensitive and specific measurement methods. In addition, different measurement principles are likely to cause differences, for example, chromatographic versus immunological techniques. However, most drug assays are based on chromatographic principles and so methodological differences may not be a major confounder when comparing *in vivo* with postmortem measurements. Nevertheless, when comparing older measurements in the literature with actual measurements, improvement in analytical methodology may be a confounding factor.

2.2. Drug stability and in vitro conversions

Some compounds are likely to be degraded in the postmortem state. Nitrobenzodiazepines are converted by bacteria to amino-compounds.[21] Some compounds such as cocaine and zopiclone are generally unstable, and the postmortem situation will then be likely to exert a greater impact, because of the less-controlled conditions for blood during a variable time period between death and blood sampling.[6,7,22] Also, in case of extensive putrefaction and body decomposition, blood may not be available or may be of a poor quality, so that drug measurements generally become unreliable. However, generally, most compounds are fairly stable when the postmortem samples have been taken with added fluoride and are stored in the frozen state.

2.3. Single dose versus steady state

For new drugs, reference may be taken to serum concentrations observed in initial pharmacokinetic studies based on only single doses. These levels will generally tend to be low compared to the situation with repeated dosing, that is, the steady-state situation with some drug accumulation.[23]

2.4. Time of sampling in relation to intake of dose

In postmortem cases, trough values are generally not obtained as under the *in vivo* therapeutic drug-monitoring situation. This factor should also be taken into account. When dosing twice during one half-life interval, for example, every 12 h for a drug with a half-life of 24 h, the difference between minimum and maximum concentrations amounts to about 40% under first-order kinetics.[23] When the dosing interval equals the half-life, the factor is about 2, that is, peak values exceed trough values by 100%. Thus, published trough values should then be doubled to take this fact into account, when dealing with the postmortem situation, where no controlled timing is present.

2.5. Inter-individual variation/presentation of published data

Generally, there is a wide variation in drug turnover rate from subject to subject. Thus, for standard doses, the range of serum concentrations observed is considerable. In some reference tables or books, only mean values are provided, not the total range, which is a factor tending to underestimate the total reference range under therapeutic conditions. In addition, for new drugs the number of subjects having been studied may be limited, so that the total range of concentrations observed under therapeutic conditions is likely to be underestimated.

2.6. Blood/serum concentration ratio

For most drugs, the distribution between the water phase and the erythrocytes is fairly even, so that the difference between serum and full blood measurements in itself is of minor importance.[6] However, for some compounds there may be a considerable difference. If a compound only penetrates into the erythrocytes to a limited degree, the serum measurements exceed the full blood measurements. This is the case, for example, THC and carbamazepine, resulting in serum concentrations equal to up to two times full blood concentrations.[6,7] Few compounds, on the other hand, are accumulated in the erythrocytes resulting in a reversed picture, for example, acetazolamide and chloroquine.[6]

2.7. Usual dose range

Initial pharmacokinetic studies may be based on smaller doses than those being gradually adopted in clinical practice. Also, dose ranges may depend on the diagnosis, for example, higher doses (e.g., fourfold) of serotonergic drugs are used for treatment of obsessive–compulsive conditions than for depression.[23] The latter diagnosis will often form the basis for establishment of therapeutic intervals, which then are misleading in relation to cases involving obsessive–compulsive disorders. For anaesthetic drugs, it should be clarified whether a stated interval refers to full anaesthesia with presumed assisted ventilation, or whether the reference interval refers to drug abuse. This is of relevance for ketamine and some other drugs.

2.8. Tolerance development

Illegal substances and medical drugs subject to abuse such as opioids are subject to the development of tolerance, which results in the use of higher doses. Supposing linear kinetics, the measured drug concentrations increase proportionally with the dose. In the case of opioids, regular pain treatment may involve increases in daily dose of perhaps up to factors 10–25, and accordingly similar increases in the serum concentrations/postmortem blood concentrations occur.[24] Thus, both in the *in vivo* and postmortem situations, reference intervals are influenced by tolerance development, making the intervals very wide. Tolerance may also play a role for other drugs, for example, antipsychotics. Due to counter-regulation of receptors, patients in chronic therapy adapt to high drug levels that are toxic to drug-naïve subjects. This has been observed for the drug clozapine, where an ordinary dose aimed for a chronic patient induced a fatal intoxication in a drug-naïve patient.[25]

2.9. Atypical response

Atypical or paradox reactions to drugs may lead to 'intoxicated'-like states despite the presence of a usual drug level, for example, benzodiazepines and alcohol.[26] Accidents leading to death may then occur because of bizarre behaviour. Thus, even though a drug concentration is in the usual level, the drug may have been indirectly contributing to death.

2.10. Postmortem sampling conditions

It is generally recommended to use femoral blood. It is important to avoid contamination with central blood. Evaluation of