Reference postmortem concentrations of antidepressant drugs reflected in a therapeutic material

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AIMS: The purpose of this work was to use a strategy to explore postmortem femoral blood concentrations in order to produce reference levels of antidepressant drugs for fatal intoxications and postmortem controls. We also wanted to compare these concentrations with those found in a therapeutic drug monitoring (TDM) material.

METHODS: During 1992-2005, femoral blood was collected at all medicolegal autopsies in Sweden. In approx. 95% of the cases, toxicology was requested, which included analysis for antidepressant drugs with a repeatedly validated GC method. The blood sampling and handling procedures were strictly standardized. Fifteen antidepressant drugs were identified in 8,591 femoral blood samples. The Swedish national forensic pathology database was used to identify cases meeting inclusion criteria as follows. For fatal intoxications, cases assigned with ICD-9 codes indicating poisoning at position 1a (immediate cause of death), were included. For postmortem controls, only diagnoses implying a death, where the victim obviously was not incapacitated due to influence of drugs, were accepted. All individual cases in each group was then consistently evaluated by two of the authors, independently. The intoxication cases were classified as single substance intoxications ("A-cases") or multiple drug intoxications ("B-cases"). After unblinding, each case with a deviating result between the authors, or presenting with an extremely high or low level, was scrutinized. This evaluation process was preceded by a compilation of TDM-data collected during 1999-2005 (n=18,610). Hence, before evaluation of the postmortem data, a rough estimate of concentrations typically indicating no toxic effects, were established to form "cut off"-levels. The serum samples of the TDM-cases were in most cases trough values in steady state with a known daily dose. Deliberate or unintentional overdoses were excluded.

RESULTS: A vast majority of the 8,591 forensic samples originally included had to be excluded due to the strict inclusion criteria. Finally, 2,707 postmortem cases were included (A, n = 330; B, n= 865; C, n = 1,801) and 18,610 TDM cases. By design, a case could only be represented once in Group A, whereas in Group B, certain cases could be represented in different substance groups due to the co-presence of several antidepressant drugs. The same applied to the C-cases. The strategy allowed for a compilation of the femoral blood concentrations of each drug in the following groups:

Group A: Certified death by intoxication with one drug only. The influence of ethanol (only BAC < 0,1% was accepted) or other substances, as well as other contributory factors, could clearly be ruled out.
Group B: Certified death by intoxication with more than one drug and/or with drug/s in combination with a significant concentration of ethanol (BAC ≥ 0,1%).

Group C: Certified other cause of death, where the circumstances excluded incapacitation by drugs.
Group T: Therapeutic drug concentrations observed in a heterogenic patient population.

For 12 of the 15 parent compounds, no overlap was seen between the 90th precentile of the concentrations in the C-cases and the 10th percentile of the concentrations of the A- or B-cases. For the metabolites, the corresponding overlap was more common. For only two substances, there was a corresponding overlap between the metabolite:parent compound ratio. Comparisons regarding the reference levels with a previous compilation of a smaller material showed that similar values were obtained. Generally, T-levelse were lower than C-levels.

CONCLUSIONS: The evaluation of the proposed strategy suggests that the reference values for fatal intoxications and non-intoxications can be reproduced, and that inter-observatory results were very similar. Further, in addition to providing reference levels for each drug, the results may also be used to produce measures of toxicity supplementary to the standard fatal toxicity index.

KEYWORDS: *Postmortem concentration, Antidepressants, Forensic chemistry, Strategy*

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