Dear editor,

we write this letter in response to an article published in Soudní Lékařství last year.

The article entitled: "An autopsy case of heatstroke under the influence of psychotropic drugs" reports the effect of antipsychotics on severe hyperthermia and death (1). The authors collected blood samples at autopsy and toxicological investigation. Their results are summarized in Table 1 (1).

They conclude that the toxic concentration of olanzapine, along with the therapeutic concentration of levomepromazine, may have caused the death of the patient, without any influence of flunitrazepam and nitrazepam (1). We object to such a conclusion, as it defies the modern view on interpretation of postmortem concentrations of drugs in blood (2,3). We assume the blood was collected from the femoral vein.

First, we find inadequate to use (4) as a sole reference for interpretation of postmortem blood concentrations. Schulz and colleagues present intravital data and case reports in their article (4). We would recommend using updated reference values for psychotherapeutics given by Hiemke et al. (5). Notably, these authors introduce the term "laboratory alert level" instead of the toxic range, which we – in accordance with clinical experience – consider more suitable (5). We would also prefer to exploit the findings from articles by Launiainen and Ketola, who give comprehensive data obtained from over 100 000 autopsies (2,3). Using this information, the reader can see, that drugs such as levomepromazine and olanzapine undergo massive postmortem redistribution (PMR), thus shifting the concentrations reported in the present paper to subtoxic ranges.

Second, nitrazepam and flunitrazepam are probably not prone to PMR, same as other benzodiazepines. Therefore, their concentration should be interpreted as toxicologically unneglectable and accordingly should be considered for their sedative properties.

Consequently, we propose another toxicological conclusion to the present case: The patient was likely not intoxicated by olanzapine, but given the detected medication, might have been sedated due to the fast-acting benzodiazepines consumption. The therapy by olanzapine and levomepromazine might have indeed disrupted thermoregulation in the patient and thus might have contributed to the hyperthermia observed in autopsy.

Yours sincerely,

PharmDr. Vít Šesták, Ph.D.*
vit.sestak@fnhk.cz, Institute of Clinical Biochemistry and Diagnostics, University hospital Hradec Králové, Sokolská 581, Hradec Králové, 500 05
RNDr. Martin Mžik, Ph.D.
Institute of Clinical Biochemistry and Diagnostics, University hospital Hradec Králové, Sokolská 581, Hradec Králové, 500 05
Prof. MUDr. Petr Hejna, Ph.D., MBA
Department of Forensic Medicine, University hospital Hradec Králové, Sokolská 581, Hradec Králové, 500 05

LITERATURE

1. **Kinoshita H, Tanaka N, Kumihashi M, et al.** An autopsy case of heatstroke under the influence of psychotropic drugs *Soud Lek* 2020; 65(4): 76-78.
2. **Launiainen T, Ojanperä I.** Drug concentrations in post-mortem femoral blood compared with therapeutic concentrations in plasma. *Drug Test Anal* 2014; 6(4): 308-316.
3. **Ketola R, Ojanperä I.** Summary statistics for drug concentrations in post-mortem femoral blood representing all causes of death. *Drug Test Anal* 2019; 11(9): 1-12.
4. **Schulz M, Iwersen-Bergmann S, Andersen H, et al.** Therapeutic and toxic blood concentration of nearly 1 000 drugs and other xenobiotics. *Crit Care* 2012; 16: R136.
5. **Hiemke C, Bergemann N, Clement HW, et al.** Consensus guidelines for therapeutic drug monitoring in Neuropsychopharmacology: Update 2017. *Pharmacopsychiatry* 2018; 51(1-02): 9-62.

AUTHOR'S RESPONSE

We thank Dr. Šesták, Dr. Mžik and Prof. Dr. Hejna for their comments regarding our recent case report (1). We collected a blood sample from the femoral vein and subjected it to toxicological analysis. As you may be aware, Schulz's article not only includes biological data, but also postmortem data, and we have used their study as a reference (2). Although "toxic concentration" is widely used in the literature (3,4), it may be important to consider using "laboratory alert level", as you recommended.

In addition, thank you for suggesting several useful references (5,6), which showed that the median drug concentration is generally likely to reflect normal postmortem (PM) concentrations. Specifically, Launiainen and Ojanperä showed that the normal PM concentrations of levomepromazine and olanzapine were approximately 0.40 µg/ml and 0.20 µg/ml, respectively (5). Further, Söderberg et al. showed that the median PM concentration of olanzapine was 0.10 µg/ml and that the 90th percentile was 0.20 µg/ml in a non-intoxication group (6,7). The minimum toxic concentration of olanzapine is given as 0.1 µg/ml (3). Based on these studies, the PM concentration of olanzapine in the present case exceeded therapeutic levels (1). The PM concentration of levomepromazine was around the "normal" PM concentration.

Since both 7-aminoflunitrazepam and 7-aminonitrazepam are pharmacologically inactive metabolites (3), they can be used as markers of ingestion for each parent drug (8). However, the detection of these metabolites does not always indicate that these drugs

have been taken just before death. In the present case, flunitrazepam and nitrazepam, the parent drugs of 7-aminoflunitrazepam and 7-aminonitrazepam, respectively, were not detected at all. I am afraid that speculating which drug was consumed based solely on the metabolites detected could result in misinterpretation.

We are familiar with the concept of postmortem redistribution (PMR). As you mentioned, PMR does not occur with nitrobenzodiazepines such as nitrazepam, flunitrazepam and their metabolites (9). However, heart/femoral nitrazepam concentration ratios of 1.95-2.16 have been reported (10).

In the present case, a relatively high concentration of olanzapine was observed (1). Olanzapine is metabolized by cytochrome p450 (CYP)1A2 and CYP2D6 (11), and levomepromazine inhibits CYP2D6, CYP1A2 and CYP3A4, in vivo (12). If anything, we may have to consider drug-drug interactions between these two drugs and further investigation may be necessary.

Yours sincerely,

Hiroshi Kinoshita, M.D., Ph.D.
Naoko Tanaka, Ph.D.
Department of Forensic Medicine, Faculty of Medicine, Kagawa University,
Kagawa 761-0793, Japan

Mitsuru Kumihashi, Ph.D.
Forensic Science Laboratory, Kagawa Prefectural Police Headquarters,
Kagawa 760-8579, Japan

Asuka Ito, M.D., Ph.D.
Ken Nagata, M.D.
Department of Forensic Medicine, Faculty of Medicine, Kagawa University,
Kagawa 761-0793, Japan.

Kunihiko Tsutsui, M.D., Ph.D.
Health Sciences, Faculty of Medicine, Kagawa University,
Kagawa 761-0793, Japan

Shoji Kimura, M.D., Ph.D.
Department of Forensic Medicine, Faculty of Medicine, Kagawa University,
Kagawa 761-0793, Japan

REFERENCES

1. **Kinoshita H, Tanaka N, Kumihashi M, et al.** An autopsy case of heatstroke under the influence of psychotropic drugs. *Soud Lek* 2020; 64: 76-78.
2. **Schulz M, Iwersen-Bergman S, Andersen H, et al.** Therapeutic and toxic blood concentration of nearly 1000 drugs and other xenobiotics. *Crit Care* 2012; 16: R136.
3. **Moffat AC, Osselton MD, Widdop B, Watts J,** *eds*. Clarke's analysis of drug and poisons (4th ed). London, Chicago: Phramaceutical Press; 2011.
4. **Molina DK.** Handbook of forensic toxicology for medical examiners. Boca Raton: CRC Press; 2010.
5. **Launiainen T, Ojanperä I.** Drug concentrations in post-mortem femoral blood compared with therapeutic concentrations in plasma. *Drug Test Anal* 2014; 6: 308-316.
6. **Ketola RA, Ojanperä I.** Summary statistics for drug concentrations in post-mortem femoral blood representing all causes of death. *Drug Test Anal* 2019; 11: 1326-1337.
7. **Söderberg C, Wernvik E, Tillmar A, et al.** Antipsychotics – postmortem fatal and non-fatal reference concentrations. *Forensic Sci Int* 2016; 266: 91-101.
8. **Drummer OH, Syrjanen ML, Cordner SM.** Death involving the benzodiazepine flunitrazepam. *Am J Forensic Med Pathol* 1993; 14: 238-243.
9. **Robertson MD, Drummer OH.** Postmortem distribution and redistribution of nitrobenzodiazepines in man. *J Forensic Sci* 1998; 43: 9-13.
10. **Moriya F, Hasimoto Y.** Tissue distribution of nitrazepam and 7-aminonitrazepam in a case of nitrazepam intoxication. *Forensic Sci Int* 2003; 131: 108-112.
11. **Callaghan JT, Bergstrom RF, Beasley CM.** Olanzapine. Pharmacokinetic and pharmacodynamic profile. *Clin Pharmacokinet* 1999; 37: 177-193.
12. **Basińska-Ziobroń A, Daniel WA, Wójcikowski J.** Inhibition of human cytochrome P450 isoenzymes by a phenothiazine neuroleptic levomepromazine: An in vitro study. *Phramacol Rep* 2015; 67: 1178-1182.