An autopsy case of heatstroke under the influence of psychotropic drugs

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SUMMARY
We present here a fatal case of heatstroke, involving olanzapine and levomepromazine medications. A male in his sixties was found dead in his storage room in the middle of August, with a high rectal temperature. Autopsy revealed congestion of the lungs without any specific findings. Quantitative toxicological analysis demonstrated concentrations of olanzapine, levomepromazine, 7-aminonitrazepam, and 7-aminoflunitrazepam in a femoral blood sample of 0.433 μg/mL, 0.177 μg/mL, 0.604 μg/mL, and 0.041 μg/mL, respectively. The concentration of olanzapine exceeded toxic levels; however, levomepromazine level was within the therapeutic range. Due to the blocking mechanism of both olanzapine and levomepromazine against muscarinic receptors, they might depress sweating and impair heat dissipation. Based on autopsy findings, results of toxicological examination, and investigation by the authorities, we concluded that the cause of death was heatstroke under the influence of olanzapine and levomepromazine.

Keywords: olanzapine – levomepromazine – heatstroke

Případ úpalu pod vlivem psychotropních látek

SOUHRN
V článku prezentujeme fatální případ úpalu po požití olanzapinu a levomepromazinu. V polovině srpna byl ve své skladištní místnosti v Japonsku nalezen muž bez známek života. V době ohledání, přibližně sedm hodin po jeho smrti, měl rektální teplotu 40,1°C. Teplota okolního prostředí byla 30,2°C, nejvyšší teplota v místnosti v průběhu dne dosahovala 36°C. Histopatologické nálezy prokázaly hyperkontrahovaná vlákna v kosterních svalech. Kvantitativní toxikologická analýza pomocí tandemové hmotnostní spektrometrie s kapalinovou chromatografií (LC-MS/MS) odhalila koncentrace olanzapinu, levomepromazinu, 7-aminonitrazepamu (metabolit nitrazepamu) a 7-aminoflunitrazepamu (metabolit flunitrazepamu) ve vzorku femorální krve 0,433 μg/ml, 0,177 ug/ml, 0,604 ug/ml, respektive 0,041 ug / ml. Ze vzorku post mortem odebrané krve nebyly detekovány žádné další léky ani ethanol. Koncentrace myoglobinu v moči byla 3000 ng/ml. Koncentrace olanzapinu překročila toxické hladiny; hladina levomepromazinu však byla v terapeutickém rozmezí. Protože jak olanzapin, tak levomepromazin působí blokováním muskarinových receptorů, mohou potlačit pocení a narušit odvod tepla. Na základě makroskopických pitevních nálezů, histologických nálezů svědčících o rozpadu svalů, výsledcích toxikologických vyšetření a vyšetřování úřadů jsme dospěli k závěru, že příčinou úmrtí byl úpal způsobený olanzapinem a levomepromazinem.

Klíčová slova: olanzapine – levomepromazine – úpal

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Olanzapine is an atypical antipsychotic drug with both dopamine D_2 and serotonin 5-HT_2 receptor antagonistic actions (1-3) as well as muscarinic receptor-blocking properties (2,3). Levomepromazine (methotrimeprazine) is phenothiazine derivative, a first-generation antipsychotics, used in the treatment of psychosis (4,5). It also has a pronounced sedative effect (4). Moreover, both olanzapine and levomepromazine have anticholinergic effects. These pharmacological actions presenting as dryness of the mouth and depression of sweating (5-7). In this study, we report a case of fatal heatstroke under the influence of olanzapine and levomepromazine.

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CASE REPORT

A Japanese man in his sixties (height, 178 cm; weight, 79 kg) was found dead in his storage room in the middle of August. The ambient temperature was 30.2 °C, when he was found. And the maximum air temperature of that day was 36 °C, at daytime. He had been receiving therapy for schizophrenia and prescribed olanzapine, levomepromazine, nitrazepam, and flunitrazepam. His rectal temperature was 40.1 °C at the time of police inspection, which was approximately seven hours after his death. The medicolegal autopsy revealed a slight contusion on his head. However, these were not considered contributory to the cause of death.

His heart weighed 465 g and contained 40 mL of blood without coagulum. The brain weighed 1255 g and with no injuries observed. The left and right lungs weighed 477 g and 515 g, respectively, and were moderately congested. The stomach contained 40 mL of brownish liquid. Signs other than congestion were not evident in other organs. Histopathological findings revealed hypercontracted fibers in skeletal muscles, appearing as "opaque fibers" (Figure. 1). Furthermore, internal examination revealed no diseases. A drug screening test using an Instant-view™ panel (ALFA Scientific Designs, Poway, CA) yielded negative results. The myoglobin concentration in the urine was

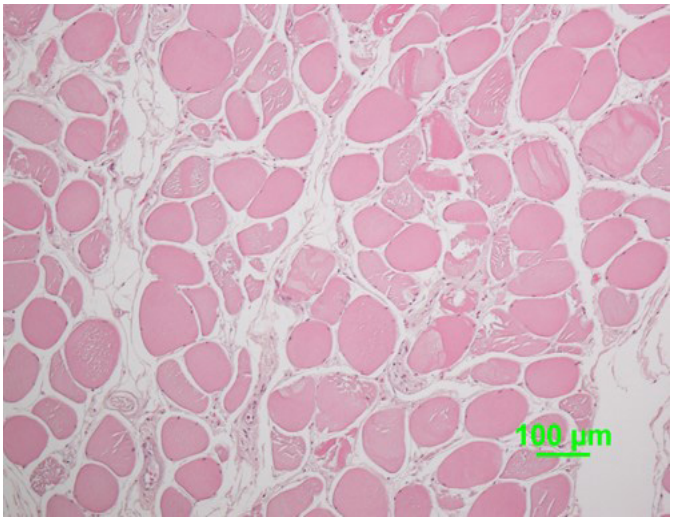

Figure 1. Hypercontracted fiber in the skeletal muscle. (diaphragm, hematoxylin and eosin staining, objective lens ; ×10).

3000 ng/ml (normal postmortem urinary myoglobin level, <50 ng/ml (8)). Postmortem blood samples were obtained for toxicological investigation.

Toxicological analysis using liquid chromatography tandem mass spectrometry (LC-MS/MS) was performed as previously described (9). In brief, the liquid chromatography separations were carried out using Ekspert™ UltraLC 100-XL (Eksigent part of Sciex, Framingham, MA, USA). An L-column2 ODS (1.5 mm × 150 mm, 5.0 µm particle size, Chemicals Evaluation and Research Institutes, Tokyo, Japan) was used with the mobile phase consisting of solvent A (5% methanol containing 10 mM ammonium formate) and solvent B (95% methanol containing 10 mM ammonium formate) with a flow rate of 0.1 mL/min. The mass spectra was obtained by a QTrap® 4500 tandem mass spectrometer (Sciex, Framingham, MA, USA). Quantitation of ethanol was performed using headspace gas chromatography.

RESULTS AND DISCUSSION

Since the morphological findings of heatstroke are usually non-specific such as the congestion of the lungs and brain edema, forensic diagnosis of heatstroke is usually based on an exclusion of other causes of death (10). In the present case, disease and trauma were excluded by the autopsy findings. The histological findings of "opaque fibers" in skeletal muscles and extremely high concentration of urinary myoglobin were attributed to muscle breakdown due to high temperature (11).

Olanzapine, levomepromazine, 7-aminonitrazepam, and 7-aminoflunitrazepam were quantitated by the toxicological examination. Table 1 shows concentrations of these substances, along with the lethal, toxic and therapeutic ranges (12-14). No other drugs or ethanol were detected.

The 7-aminonitrazepam and 7-aminoflunitrazepam are metabolites of nitrazepam and flunitrazepam, respectively. However, we could not detect both nitrazepam and flunitrazepam in the present case. Since nitrazepam and flunitrazepam are converted to 7-amino metabolites after death (15), the pharmacological properties of these drugs were evaluated as the sum of the concentration of each parent drug and its metabolites. In the present case, as postmortem blood concentrations of 7-aminonitrazepam and 7-aminoflunitrazepam were below lethal range (13,14), both these drugs were not likely to have significantly contributed to his death.

The diagnosis of fatal heatstroke is based not only on autopsy findings, but also with the consideration of the circumstances of the victim (10). Drugs, such as anticholinergics and phenothiazines, are predisposing factors for heatstroke (16). It has been reported that patients with schizophrenia have higher risk for heat-related illness (17). First-generation antipsychotics, such as levomepromazine and chlorpromazine, are risk factors of heatstroke (17,18), and second-generation antipsychotic olanzapine is also implicated to drug-induced fever in the absence of neuroleptic malignant syndrome (19). Since the present case occurred in the middle of summer, the pharmacological effect of antipsychotic drugs with anticholinergic properties that he was receiving might have potentiated heat accumulation and impairment of heat dissipation.

Blood levels of olanzapine was over the therapeutic range (0.433 µg/ml). Olanzapine has a potent antagonistic action to dopamine D_2 receptor (2,3), and it may impair thermoregulation and decrease heat tolerance (18,20). As both olanzapine and levomepromazine have an anticholinergic property within the range of clinical dose (7), pharmacological actions via muscarinic receptor may decrease sweating and cause impairment of heat dissipation (18,20). Although the concentration of levomepromazine is within the therapeutic range, it has a pronounced sedative effect (4). This would have decreased his ability to move away from the hot environment.

Based on the macroscopic autopsy findings, histological findings suggestive of muscle breakdown, results of toxicological examination, and investigation by the authorities, we concluded that the cause of death was heatstroke under the influence of antipsychotic drugs. Our case highlighted the fact that we need to consider the effects of prescribed drugs for forensic diagnosis.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest with regard to the publication of this paper.

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Table 1. Concentration of each drug and metabolites in the postmortem blood sample and their lethal, toxic, and therapeutic ranges (µg/ml).

Drug and metabolite	Blood	Therapeutic range	Toxic range	Lethal range	[reference]
7-aminoflunitrazepam	0.041	-	-	0.27–1.27	[13]
7-aminonitrazepam	0.604	-	-	1.56	[14]
Levomepromazine	0.177	0.005–0.2	0.4	0.5	[12]
Olanzapine	0.433	0.02–0.08	0.15–0.2	0.25–4.9	[12]

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