Online publication ahead of print, AJMHS Vol 64, 2024

# An Autopsy Case of Heatstroke under the Influence of Anticholinergic Drugs

Sella Takei[1], Hiroshi Kinoshita[2*], Mostofa Jamal[1], Tadayoshi Yamashita[1], Etsuko Tanaka[1], Sachiko Kawahara[1], Takehiko Murase[1]

[1] Department of Forensic Medicine, Faculty of Medicine, Kagawa University, Japan
[2] National Research Institute of Police Science, Japan

**Abstract**

A case of fatal heatstroke involving atropine, chlorpheniramine and pseudoephedrine is presented. Autopsy revealed congestion of lung and histological findings of hypercontracted fibers in skeletal muscle. Quantitative toxicological analysis revealed concentrations of atropine and chlorpheniramine in femoral blood sample to be 0.02 μg/mL and 0.30 μg/mL, respectively, and both were below fatal levels. Pseudoephedrine was also identified, but not quantified. From the autopsy findings, results of toxicological examination and investigation by the authorities, we concluded that the cause of death was heatstroke under the influence of atropine and chlorpheniramine.

**Keywords**: atropine, chlorpheniramine, pseudoephedrine, heatstroke

**Address for correspondence:** National Research Institute of Police Science, 6-3-1, Kashiwanoha, kashiwa, Chiba, 277-0882, Japan. E-mail: kinoshita@nrips.go.jp

## INTRODUCTION

Atropine is an alkaloid derived from *Atropa belladonna*. This potent anticholinergic agent shows pharmacological actions such as cardiac slowing, dryness of the mouth, and inhibition of sweating. Atropine is clinically used as preanesthetic medication, a relaxant of the gastrointestinal tract or an antidote to organophosphate insecticide poisoning (1). Chlorpheniramine is a sedative histamine $H_1$-receptor antagonist, used in decongestants, antitussives, and expectorants with other components (2). Pseudoephedrine, an optical isomer of ephedrine, is used as a nasal decongestant and bronchodilator (3). These components are commonly used in over-the-counter (OTC) cold and allergy drugs.

Here we report a case of fatal heatstroke under the influence of atropine and chlorpheniramine.

## CASE REPORT

A Japanese male in his twenties (height, 153 cm; weight, 59.5 kg) was found dead in his room in late July. Numerous (approximately 60) empty packets of non-prescribed decongestant drugs, containing atropine, chlorpheniramine and pseudoephedrine, were found in his room during investigation by the authorities. Rectal temperature was 40.3C at the time of inspection by the police, approximately 4 hours after his death. Medico-legal autopsy revealed slight contusions on his leg, but these were not considered contributory to the cause of death.

The heart weighed 330 g and contained 275 mL of slightly viscous blood without coagulum. The brain weighed 1400 g and was edematous. The left and right lungs weighed 432 g and 439 g, respectively, and were moderately congested. The stomach contained 60 mL of brownish liquid. Histopathological findings revealed congestion of the lungs and hypercontracted fibers in skeletal muscle appearing as “opaque fiber” (Fig. 1). Internal examination revealed no diseases. Signs other than congestion were not noted in other organs. A drug screening test using a Triage™ panel (Biosite Diagnostic, San Diego, CA) yielded negative results. The concentration of myoglobin in urine was over 3000 ng/ml (normal postmortem urinary myoglobin level, <50 ng/ml (4)). Postmortem blood and urine were collected for toxicological investigation.

Toxicological analysis using a 6890N gas chromatograph (GC) combined with a 5973 MS mass spectrometer (Agilent Technologies, Santa Clara, CA) was performed using a slight modification of the method described in a previous report (5). Quantitation of ethanol was performed using headspace gas chromatography.

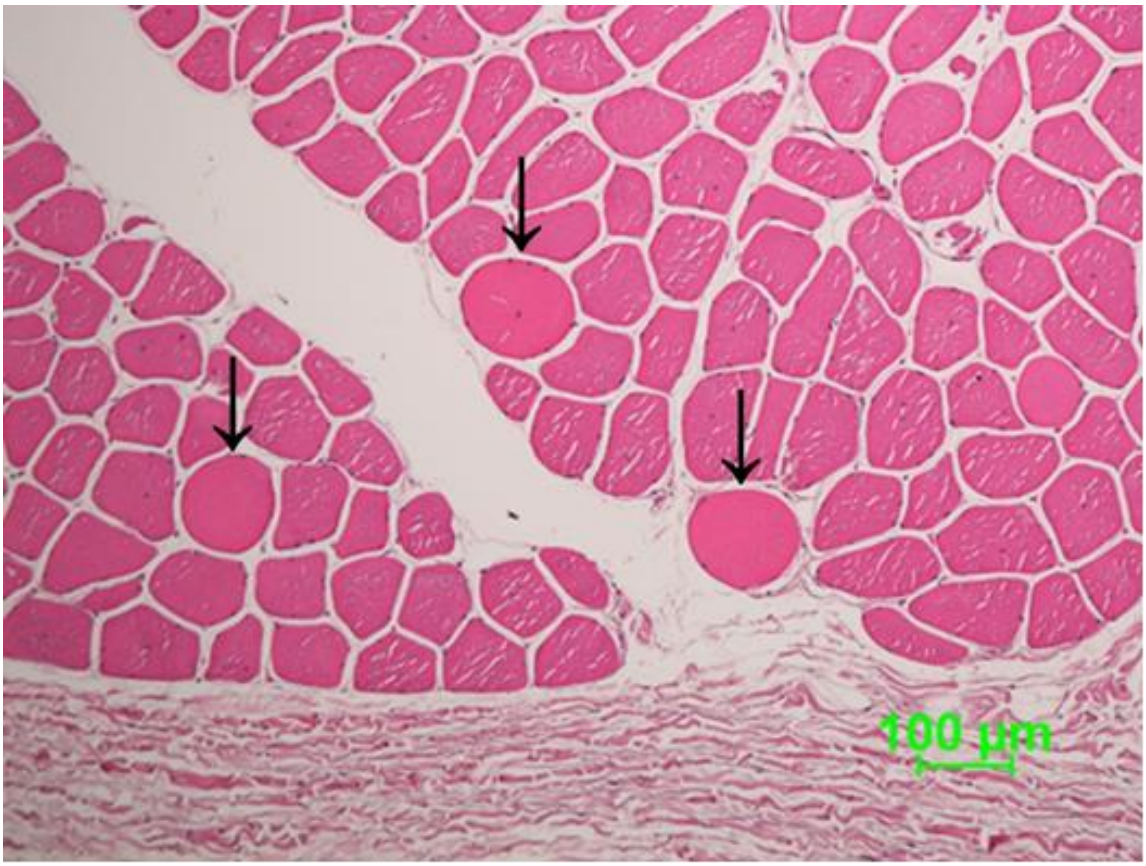


**Figure 1.** Hypercontracted fiber in skeletal muscle (arrow)
(rectus abdominis muscle, hematoxylin and eosin staining, objective lens; x10).

## RESULTS AND DISCUSSION

Diagnosis of heatstroke is usually based on an exclusion of other causes of death (6). In the present case, disease and trauma were excluded by the autopsy findings. The morphological findings of heatstroke, such as congestion of the lungs and brain edema, are usually non-specific (6). The histological finding of "opaque fiber" in skeletal muscle and extremely high concentration of urinary myoglobin were attributed to rhabdomyolysis, caused by damage to muscle tissue due to high temperature and tissue hypoxia (7).

Toxicological analysis identified atropine, chlorpheniramine and pseudoephedrine in each sample. Table 1 shows concentrations in postmortem blood and urine samples, along with the currently established lethal, toxic and therapeutic levels (8).

**Table 1.** Drug concentration in each sample (μg/ml)

| | Blood | Urine | Therapeutic | Toxic | Fatal |
|---|---|---|---|---|---|
| Atropine | 0.02 | 0.34 | 0.002-0.025 | 0.03-0.1 | 0.2 |
| Chlorpheniramine | 0.3 | 2.5 | 0.003-0.017 | - | 1.1 |
| Pseudoephedrine | + | + | | | |

+ : qualitative alone

Quantification of pseudoephedrine was not performed. No other drugs or ethanol were detected from postmortem samples.

OTC drugs containing chlorpheniramine or pseudoephedrine are sometimes abused (9,10). Blood levels of chlorpheniramine at the time of death were far beyond the therapeutic range, but not within the fatal range (Table 1). This drug includes stimulation of the central nervous system as a side effect (11). As a first-generation H1-antagonist, chlorpheniramine shows atropine-like actions via muscarinic receptors (11). Atropine is a potent anticholinergic drug that shows inhibitory effects on sweating (12). This effect would appear at the relatively low dose of 0.5 mg (12), and the estimated blood level was 0.0023-0.0036 μg/ml, using values of distribution volume (Vd) for atropine (2.3-3.6 L/kg) (1) and the victim's body weight. The concentration of atropine in blood in the present case was relatively higher, although still within the therapeutic range. The pharmacological actions of both drugs induce decreased sweating and cause severe heat accumulation.

As heatstroke can be induced under various conditions, the diagnosis of fatal hyperpyrexia is based on not only autopsy findings, but with consideration of the circumstances of the victim (6). Reported predisposing factors for heat stroke are pre-existing diseases, pharmaceuticals, and constitutional factors (6,13,14). The present case occurred in the middle of summer, and sweating would have been strongly suppressed by the overdosing of anticholinergic agents, both atropine and chlorpheniramine. Such conditions potentiate heat accumulation, as anticholinergic and antihistamine drugs are predisposing factors (6,13,14).

Based on the macroscopic autopsy findings, findings of rhabdomyolysis, results of toxicological examinations and investigation by the authorities, we concluded that the cause of death was heatstroke. Our results indicate that the victim died following ingestion of massive doses of atropine and chlorpheniramine. We have to consider the effects of these drugs for forensic diagnosis.

**Acknowledgements**: None declared.

**Conflict of Interest Statement**: The author declares that have no conflict of interest.

**REFERENCES**

1. Baselt RC. Atropine. In: Disposition of toxic drugs and chemicals in man. 8th ed. Foster City: Biomedical Publications 2008: 127-129.

2. Baselt RC. Chlorpheniramine. In: Disposition of toxic drugs and chemicals in man. 8th ed. Foster City: Biomedical Publications 2008: 288-290.

3. Baselt RC. Pseudoepherine. In: Disposition of toxic drugs and chemicals in man. 8th ed. Foster City: Biomedical Publications 2008: 1344-1346.

4. Zhu BL, Ishida K, Quan L, Taniguchi M, Oritani S, Kamikodai Y, et al. Post-mortem urinary myoglobin levels with reference to the causes of death. Forensic Sci Int 2001; 115: 183-188.

5. Kudo K, Ishida T, Hikiji W, Hayashida M, Uekusa K, Usumoto Y, et al. Construction of calibration-locking databases for rapid and reliable drug screening by gas chromatography-mass spectrometry. Forensic Toxicol 2009; 27: 21-31.

6. Madea B. Injuries due to heat. In: Handbook of forensic medicine. Madea B, ed. West Sussex: Wiley Blackwell; 2014: 451-467.

7. Kinoshita H, Kubota A, Nishiguchi M, Ouchi H, Minami T, Yamamura T, et al. Three autopsy cases of heat illness. Res Pract Forens Med 2005; 48: 173-177.

8. Schulz M, Iwersen-Bergmann S, Andresen H, Schmoldt A. Therapeutic and toxic blood concentrations of nearly 1000 drugs and other xenobiotics. Crit Care 2012; 16: R136.

9. Hira K. The knowledge about ingredients of nonprescription drugs is important in the clinical practice for patients with drug abuse / dependence. Japanese Journal of Psychiatric Treatment 2017; 32: 1501-1505.

10. Ito K, Koyama T. Abuse of ephedrine and pseudoephedrine. Schizophrenia Frontier 2010; 11: 123-127.

11. Skidgel RA, Erdös EG. Histamine, bradykinin and their antagonists. In: Brunton LL, Lazo JS, Parker KL, editors. Goodman & Gilman's The pharmacological basis of therapeutics 11th eds. New York, Chicago: McGraw-Hill; 2006: 629-651.

12. Brown JH, Taylor P. Muscarinic receptor agonist and antagonist. In: Brunton LL, Lazo JS, Parker KL, editors. Goodman & Gilman's The pharmacological basis of therapeutics 11th eds. New York, Chicago: McGraw-Hill; 2006: 183-200.

13. Green H, Gilbert J, James R, Byard RW. An analysis of factors contributing to a series of deaths caused by exposure to high environmental temperatures. Am J Forensic Med Pathol 2001; 22: 196-199.

14. Grogan H, Hopkins PM. Heat stroke: implications for critical care and anesthesia. Br J Anesth 2002; 88: 700-707.