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Effects of chronic administrations of aconitine on body weight and rectal temperature in mice

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Abstract

Aconitine, a major *Aconitum* alkaloid, is well known for its high toxicity that induces severe arrhythmias leading to death. However, aconitine has been used as one of the most popular compounds in Shino-Japanese traditional herbal medicine. Little has been reported concerned with the long-term effects of aconitine. Therefore, the authors investigated the physiological effects of chronic administrations of aconitine by determining the changes in body weight and rectal temperature of mice, compared with the concentrations of aconitine and its metabolites (benzoylaconine and aconine) in the liver and kidneys. The concentration ratio of aconitine to the total *Aconitum* alkaloids (from day 0 to 22; 90 min after the last administration) gradually decreased, whereas its metabolites increased until day 22. The body weight gain in aconitine-administered group was less than that of the control group until day 22. Transient rectal hypothermia occurred within 30 min after the last administration of aconitine. Then the rectal temperature gradually increased to normal level in respect to time. This study might reveal the possibilities that the drug metabolism of aconitine increased and the toxicity of aconitine decreased due to long-term administrations of aconitine.
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Keywords: Aconitine; Chronic administration; Body weight; Rectal temperature

1. Introduction

Aconitum plants (Ranunculaceae family) are widely distributed in the cooler regions or mountains of the northern hemisphere (Bisset, 1981). Aconitine is an *Aconitum* alkaloid produced by the plant *Aconitum napellus*. "Bushi" or "Uzu", which has been one of the most popular compounds in Shino-Japanese traditional herbal medicine (Kampo-Medicine), contains aconitine (Bisset, 1981). In Europe, *Aconitum* alkaloids have also been used in homeopathic medicine (called "Aconite"). In Shino-Japanese traditional herbal medicine, the indications for treatment with *Aconitum* alkaloids are patients complaining of pain, coldness of distal extremities, recurrent cold episodes, heavily dressed in comparison to individuals of the general public, low basal body temperature, vertigo, and general fatigue, for example (Hara, 2002; Imadaya and Ohno, 2003). The patients with chronic diseases are often administered with *Aconitum* alkaloids for long periods. Aconitine is a major toxic *Aconitum* alkaloid. It induces severe arrhythmias with final outcome leading to death (Scherf, 1947; Camps, 1968; Bhargava et al., 1969; Vaughan Williams, 1975; Catterall, 1980; Tai et al., 1992; Dickens, 1994; Mizugaki et al., 1998). The lethal dose 50% (LD_{50}) of aconitine for mice is 1.8 mg/kg (single-dose, orally) (Ohno, 1998), and 1–2 mg for humans (single-dose, orally) (Camps, 1968; Rentoul and Smith, 1973). In 1995, a medicolegal autopsy was performed on an adult male that had been administered aconitine daily for a few months in Saitama Prefecture, Japan. He complained of variable symptoms to his friends prior to his death. The authors detected *Aconitum* alkaloids from his organ samples. There are many studies that report on the single-dose effect of aconitine. However, no reports were available that reported on the long-term effect of aconitine, most likely due to its high toxicity. The authors have previously reported on the effects of long-term administrations of aconitine on electrocardiogram and tissue concentrations of aconitine and its metabolites (benzoylaconine and aconine) (Fig. 1) in

Abbreviations: LD_{50}, lethal dose 50%; BSTFA, Bis (trimethylsilyl) trifluoroacetimide; TMCS, trimethylchlorosilane; ICR, Institute of Cancer Research; GC/MS, gas chromatography/mass spectrometry; S.E.M., standard erroe of mean; ANOVA, analysis of variance; p.o., per os; i.p., intraperitoneal; i.v., intravenous; ND, not done

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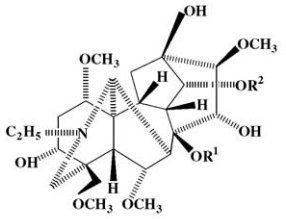

	R^1	R^2
Aconitine	$COCH_3$	COC_6H_5
Benzoylaconine	H	COC_6H_5
Aconine	H	H

Fig. 1. Chemical structures of *Aconitum* alkaloids.

mice (Wada et al., 2005). In this report, the authors report the effects of chronic administrations of aconitine on body weight and rectal temperature in mice. As aconitine has acute and high toxicity, it is so difficult to examine the effects of aconitine on human experimentation. For this reason, the authors designed this study to investigate the effects of aconitine in experimental animal models. This study might contribute valuable information not only to forensic toxicology but also to traditional herbal medicine.

2. Materials and methods

2.1. Reagents

Aconitine and hypaconitine were purchased from Sigma Chemical Co. (St. Louis, MO, USA), benzoylaconine and aconine from Sanwa Shoyaku (Tochigi, Japan), N,O-Bis (trimethylsilyl) trifluoroacetimide (BSTFA) with 1% trimethylchlorosilane (TMCS) from Pierce Chemical Co. (Rockford, IL, USA), and Bond Elut Silica (Si) cartridges from Varian Inc. (Harbor City, CA, USA). Other solvents used were of analytical grade.

2.2. Animals

Male mice of the Institute of Cancer Research (ICR) strain (age, 5 weeks; weighing 29–33 g; Nippon Bio-supp. Center, Tokyo, Japan) were used for animal experiments, which were conducted according to the guidelines of the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals and approved by the Nippon Medical School (Tokyo, Japan) Review Boards (# 14–32).

2.3. Administraton of drugs

The mice of the ICR were divided into two study groups: the aconitine-administered group and the control group.

Aconitine was dissolved in 0.1 M acetate buffer (pH 5.0) and a total volume of 1 mg/kg per day was administered to the animals of the aconitine-administered group orally. The mice of the control group were administered only with acetate buffer instead of aconitine to serve as controls. The drugs and buffer were administered to the mice with autoclaved stomach tubes once daily in the morning for a maximum of 22 days.

2.4. Preparation of the test samples

The mice of the aconitine-administered group were sacrificed on days 0, 1, 3, 7, 10, 15, 19, and 22 (90 min after the last administration of the drug; $n = 3$, respectively). Samples of liver and kidneys were immediately excised and stored at −80 °C until analysis.

2.5. Body weight

The body weight of the mice during the experiment was determined before administering aconitine and food every morning ($n = 5$, respectively).

2.6. Rectal temperature

The rectal temperature of the mice was determined with a digital thermometer AD-5602 (A and Day Co., Tokyo, Japan) at the distance of 2.5 mm from the anus. The measurement was performed at room temperature of 24.0 °C. Mice with normal rectal temperature 37.0–38.0 °C were selected and used in the experiment. The rectal temperature was measured at 10-min intervals, totaling 90 min after the last administration of aconitine on days 0, 1, 3, 7, 11, 15, 19, and 22 ($n = 5$, respectively).

2.7. Analysis

Preparation of sample: the samples were prepared according to the previous report (Wada et al., 2005). Liver or kidney was extracted with ethanol and then solid phase extraction was conducted using Bond Elut Si column. Following the extraction, gas chromatography/mass spectrometry (GC/MS) analysis was performed.

The values of total *Aconitum* alkaloids (the sum total of aconitine, benzoylaconine, and aconine) were calculated. In addition, the ratios of aconitine versus total alkaloids, benzoylaconine versus total alkaloids, and aconine versus total alkaloids were calculated.

2.8. Statistics

Data are represented as the mean ± standard error of mean (S.E.M.). As for statistical analysis, in cases of non-repeated measurement, the one-factor (time) analysis of variance (one-factor ANOVA) with post hoc testing for group differences was employed. In cases of repeated measurement, repeated measures ANOVA was employed. All the statistical analyses were performed using the standard statistics software SPSS, version 11.5 (SPSS, Inc., Chicago, IL, USA). Differences were considered to be significant when *P*-values were less than 0.05.

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