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Case Report

2,4-Dinitrophenol: A threat to Chinese body-conscious groups

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Abstract

2,4-Dinitrophenol (2,4-DNP), a yellowish compound, has historically been used in the manufacture of dyes, explosives, and fungicides. As it uncouples mitochondrial oxidative phosphorylation, the compound was also used as an antiobesity agent early in the past century. The compound was subsequently banned by the United States Food and Drug Administration in 1938 due to its potentially fatal adverse effects, including hyperthermia, cataract, agranulocytosis, hepatoxicity, nephrotoxicity, and cardiotoxicity. However, the popularity of 2,4-DNP as a slimming aid has appeared to increase again in recent years. The Hong Kong Hospital Authority Toxicology Reference Laboratory recently confirmed two cases of self-administered 2,4-DNP with different clinical presentations to hospitals in the area. Here we describe those two cases, in an attempt to underscore the potential of misuse of this substance by body-conscious groups among the Chinese population.

Keywords: 2,4-dinitrophenol; bodybuilding; slimming; uncoupling agents

1. Introduction

2,4-Dinitrophenol (2,4-DNP) is a crystalline solid that is slightly soluble in water, and more soluble in organic solvents such as ethanol and ether.[1] The chemical has been used as a component of explosives and fungicides; with its yellow color, it has also been used in fabric and food colorings since the late 19th century.[2]

Subacute and acute 2,4-DNP compound poisoning cases were reported among workers in munitions factories during World War I, which included fatalities.[3] Clinical symptoms include anorexia, nausea, vomiting, headache, dizziness, respiratory distress, as well as generalized weakness and weight loss. Profuse yellow-tinted sweating is pathognomonic of this poisoning.[4] Hyperthermia was a commonly observed feature insofar as the body temperature could rise up to 43°C in fatal cases. *Rigor mortis* set in promptly after death, and *post mortem* examination showed pulmonary edema with a possible yellowish tint of the organs.[3]

Since 1933, the compound had been marketed as an antiobesity agent promising substantial benefits. The use of this compound was particularly attractive when apparently only fat and carbohydrates were broken down, but not proteins, with no change in nitrogen excretion caused by 2,4-DNP.[5] This all occurred despite the warning issued by the Council on Pharmacy and Chemistry concerning the potential toxicities of the compound,[6] which inevitably resulted in some instances of uncontrolled administration.[7] At the same time, the spectrum of adverse effects from the use of 2,4-DNP expanded: these included maculopapular erythematous skin eruptions in 7% of the cases,[5] in addition to gastrointestinal discomfort, cataract, hepatoxicity, nephrotoxicity, cardiotoxicity, and agranulocytosis.[7,8] There were deaths reported following administration of the compound within the recommended dosage,[7] and the chemical was finally banned in 1938.[2]

Conflicts of interest: The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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In recent years it has been reported that the use of 2,4-DNP as a slimming agent is again on the rise.[4,9] Here we report two local cases of 2,4-DNP misuse in Hong Kong Chinese patients referred to our laboratory, in which the adverse effects of the compound led to patient hospitalization.

2. Case reports

2.1. Case 1

The 30-year-old male patient, who had a history of good health, was referred by his general practitioner to the hospital. He presented with maculopapular rash on his forehead as well as shortness of breath. He described a recent history of ingesting a type of bodybuilding pill obtained from his friend for 10 days, which caused him to sweat excessively when taken together with carbohydrate-rich food, in addition to another over-the-counter cold medication. Upon presentation his rash became generalized, involving his trunk, limbs, neck, and oral mucosa with skin sloughing. His blood pressure, pulse, and body temperature were normal (119/68 mmHg, 61 beats/minute, 36.0°C, respectively), and he had an increased respiratory rate of 18 breaths/minute. Liver and renal function tests and complete blood picture were grossly normal. Muscle enzymes were not measured. The bodybuilding pill was sent to the Hospital Authority Toxicology Reference Laboratory for chemical analysis, in which 2,4-DNP was detected by both high-performance liquid chromatography-diode array detector (HPLC-DAD) and gas chromatography-mass spectrometry; no other known drug or toxin was detected. The 2,4-DNP content of the pill was subsequently estimated by HPLC-DAD to be 72 mg/pill. The patient was discharged on Day 2, and he never returned for follow-up.

2.2. Case 2

The 25-year-old female patient, with a past history of Graves' disease in remission, complained of fever and muscle pain. She gave a recent history of taking a body slimming pill obtained from a friend for one month, who also reported similar complaints upon using the pill. On admission she was observed to have tachycardia with a heart rate of 114 beats/minute and tachypnea with a respiratory rate of 20 breaths/minute. Her body temperature was 39.7°C. Her serum-free thyroxine level was 12.8 pmol/L (reference interval 12.0–22.0 pmol/L), while her serum thyroid-stimulating hormone level was decreased to 0.14 mIU/L (0.27–4.20 mIU/L), which subsequently returned to normal (1.56 mIU/L) after 1 month without treatment. Her muscle enzymes were moderately elevated on admission: serum creatine kinase and lactate dehydrogenase concentrations were 696 U/L (42–190 U/L) and 403 U/L (211–370 U/L), respectively, which further increased to 915 U/L and 768 U/L and returned to normal after one month (55 U/L; 272 U/L). Liver and renal function tests and complete blood picture were grossly normal. The patient's body slimming pills were sent to the Hospital Authority Toxicology Reference Laboratory and analysis by HPLC-DAD and liquid chromatography-ion trap-time-of-flight mass spectrometry showed the content of 2,4-DNP; no other known drug or toxin was detected. Quantitative estimation of the 2,4-DNP content was not performed due to lack of further specimen. The patient was given paracetamol 500 mg every 4 hours for her hyperthermia and propranolol 10 mg three times daily for her tachycardia. Her symptoms subsided and she was discharged on Day 4. She was asymptomatic at her follow-up visit one month later.

3. Discussion

In this report we describe two cases of misuse of 2,4-DNP from an unknown source occurring in a Chinese population within four months. Although the causal relationships were difficult to establish, the adverse effects were temporally consistent with the use of 2,4-DNP, which appeared when use of the compound was commenced and subsided upon termination of use. It was a major limitation that no concurrent biological sample in which the presence of the compound could be confirmed, was available, and therefore we could only rely on the drug history provided by the patients. The self-administered 2,4-DNP was associated with different clinical presentations in the two cases: one patient presented with generalized skin rash and the other with hyperthermia and muscle injury. Both presentations are known adverse reactions of 2,4-DNP use. The latter was associated with its thermogenic property whereas the former was likely to be related to the immunogenic reactions towards the compound *in vivo*. Although the causal role of the compound for the rash in our patient could not be firmly established, a series of cases presenting with cutaneous reactions towards 2,4-DNP were reported in the 1930s, and it was estimated that 7% of exposed individuals were affected.[10,11] The compound was later confirmed to be a potent hapten that could produce hypersensitivity via the immunoglobulin E-mediated immune response.[12] It is now known that the compound acts by uncoupling mitochondrial oxidative phosphorylation: by increasing the proton conductance of mitochondria, and thus the basal leak pathway from cytosol into the matrix, synthesis of adenosine triphosphate is uncoupled and energy is dissipated as heat rather than in the high-energy phosphate bonds.[13] The hyperthermia produced then leads to the subsequent damage to muscle and organs, and other symptoms related to increased body temperature.

The high potential of 2,4-DNP toxicity is two-fold. First of all, with its claim of having a fat-burning effect without the need of dietary control, it attracts the immense interest of those body-conscious groups in society: these include teenage to middle-aged females, or even males, who are paying particular attention to body slimming, as well as bodybuilders who are similarly concerned about losing fat at the same time as muscle building. Secondly, the dose recommended for its fat-burning effect is close to that producing dangerous adverse reactions, thus allegedly having a narrow “therapeutic index”, as described by Hsiao et al.[9] Moreover, the dose required to produce fatality can decrease abruptly with an increase in body temperature so that the risks are particularly high in those body-conscious groups who are likely to exercise

vigorously.[14] The clinical presentation can therefore mimic heat exhaustion or heat stroke as well as other types of poisoning. Management of 2,4-DNP poisoning requires aggressive supportive measures. Consequently, cooling is important in patients with hyperthermia, whereas dialysis and hemoperfusion are not effective. If conventional cooling measures such as ice-baths and sedation with benzodiazepines are inadequate to reduce the body temperature, the use of dantrolene is also suggested by some groups.[15,16] Although people often survived after taking the compound, a number of fatal cases have been reported in the literature.[4,9,15,17]

As a slimming agent, 2,4-DNP has reportedly resurfaced, probably with the increasing convenience of purchase over the Internet.[4,9] In 2003, 70 years after Cutting et al[1,5] reported about the fat-burning properties of 2,4-DNP, the Food Standards Agency in the UK issued an urgent advisory about the use of 2,4-DNP when a Finnish body-builder was hospitalized after taking the compound. Our two cases demonstrate that the use of the compound can similarly be a threat to Chinese populations where consciousness of body image is apparent. Frontline clinicians should raise awareness for 2,4-DNP poisoning especially when the high-risk, figure-minded, and bodybuilding groups are encountered.

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