Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)
ISSN 1673-1581 (Print); ISSN 1862-1783 (Online)
www.zju.edu.cn/jzus; www.springerlink.com
E-mail: jzus@zju.edu.cn

Clinical features and treatment in patients with acute 2,4-dinitrophenol poisoning

Yuan-qiang LU[†], Jiu-kun JIANG, Wei-dong HUANG[†‡]

(*Department of Emergency, the First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310003, China*)

[†]E-mail: luyuanqiang@yahoo.cn; huangweidong2003@hotmail.com

Received July 8, 2010; Revision accepted Nov. 10, 2010; Crosschecked Jan. 26, 2011

Abstract: Objective: To report clinical features and treatment of 16 cases of acute 2,4-dinitrophenol poisoning. Methods: A total of 16 patients suffering from acute poisoning due to non-oral exposure to 2,4-dinitrophenol were sent to our hospital. Two died within 3 h after admission, while the other 14 responded to supportive treatment and hemoperfusion. Clinical features and treatment of the patients were retrospectively analyzed and presented. Results: Fourteen patients recovered and were discharged after four to six weeks of treatment. No obvious poisoning sequelae were found in the three-month follow-up. Conclusions: Non-oral exposure to 2,4-dinitrophenol is toxic. Hemoperfusion and glucocorticoid treatments may be efficient measures to prevent mortality, but this requires further study.

Key words: 2,4-Dinitrophenol, Poisoning, Therapeutics, Hemoperfusion, Glucocorticoid
doi:10.1631/jzus.B1000265 **Document code:** A **CLC number:** R135.1

1 Introduction

Dinitrophenols (C_6-H_4-N_2-O_4; Chemical Abstracts Service (CAS) No. 25550-58-7) are highly toxic chemicals with six isomeric compounds. They are widely used in dyes, developers, drugs, indicators, insecticides, and in the preservation of wood. 2,4-Dinitrophenol (2,4-DNP) (CAS No. 51-28-5), the most toxic compound, is a yellow, combustible crystalline solid that has a musty odor and is poorly soluble in water. It was used as an oral weight control drug in the 1930s, because it clearly increased the body's basal metabolic rate, but was soon banned for this purpose by the Food and Drug Administration (FDA) because of serious adverse effects such as hyperthermia, cataracts, and even death (Tainter *et al.*, 1934). In recent years, some illegal weight control drugs with 2,4-DNP can be purchased and poisoning events, even deaths, because of ingestion have been reported in some countries (Kurt *et al.*, 1986).

Since 2,4-DNP is a crystalline solid and is barely soluble in water, poisoning accidents are rare with normal protective measures other than deliberate ingestion. In this study, we report 16 patients with acute 2,4-DNP poisoning through occupational exposure due to ignorance of the risk of poisoning.

2 Materials and methods

2.1 Clinical data

In 2009, a serious incident occurred whereby 20 individuals were poisoned. Eleven, who were workers in a chemical factory, were directly exposed to 2,4-DNP (direct contact with skin and respiratory tract) with no protection at first; they only wore standard face shields after encountering the yellow powder. Another nine were their relatives, who indirectly contacted the poison while taking care of them; the contact area was limited to the forearms and hands. Of all the poisoned people, four aged 3–8 years were treated in the Children's Hospital of Zhejiang Province and 16 patients were treated in our hospital. They

[‡] Corresponding author

were 12 males and 4 females [mean age (36.6±16.5) years, range 12–46 years], and three were less than 16 years old.

The duration from exposure to onset was 2–30 h (mean 17.1 h). Clinical manifestations included flushing of skin, intense thirst, profuse perspiration, hyperpyrexia, restlessness, malaise, dyspnea, tachycardia, tachypnea, and even convulsion, muscle rigor, and coma. The mean oral temperature was 38.3 °C (range 37.8–40.7 °C), and the mean pulse rate was 80 beats/min (range 40–144 beats/min) in 16 patients. Heavy perspiration was the first symptom indicated by all patients, followed by fever, skin redness, and fatigue. Most patients (87.5%, 14/16) had shortness of breath after movement and this symptom was relieved after resting in 62.5% (10/16), while 25.0% (4/16) were not relieved by standard supportive treatment. The contaminated parts of the skin had no feeling of pain or other sensory dysfunction in all patients.

These patients were diagnosed as having acute 2,4-DNP poisoning based on the toxic exposure history, hygienic investigation at the exposure site, clinical manifestations, laboratory examination, and poison identification made by the Zhejiang Disease Control Center and the Zhejiang Public Security Division. It was difficult to accurately estimate the exposure level of each person; we could only make a rough estimate of five mild and eleven severe cases from the exposure time, the type of contact, the degree of skin contamination, and clinical symptoms. However, two severe patients had notable hyperpyrexia with respective body temperatures of 40.7 and 39.8 °C, convulsions, muscle rigidity, and disturbance of consciousness. They were Babinski negative, and death suddenly occurred within 12 h after the onset of symptoms.

2.2 Treatment

Basic treatment was to remove and isolate the polluted clothing, and cut off the contaminated hair and nails. During the rescue, we also tried water, soap, and alcohol to remove the 2,4-DNP dust, without success. Because there is no antidote, all patients received physical cooling with ice bags, symptomatic and supportive treatments including electrocardiogram monitoring, oxygen therapy, and water, electrolyte, and acid-base balance maintaining by administering normal saline and Ringer's solution. Antioxidants such as intravenous glutathione (GSH), and large doses of vitamins C and E were used during the treatment. Except the two deaths, nine severe cases were given 500 mg/d of methylprednisolone for 3–5 d. Thereafter the dose was decreased gradually and stopped at 8–10 d. As for the five cases with mild symptoms, a dose of 40–80 mg/d was given for 3 d. and was gradually reduced until ceasing at 6–7 d. Hemoperfusion (HP) was applied to the patients within 6 h of admission. Styrene/divinylbenzene copolymer (HA330 macroporous resin, Zhuhai Lizhu Biomedical Materials Co., Guangdong, China) processes a large capacity at a rapid rate, and has good blood compatibility. The five cases with mild symptoms were treated once a day (4–6 h) for three consecutive days, while the nine severe cases were treated once a day (6–8 h) for 6 d. In addition, one case who suffered neutropenia received recombination human granulocyte colony-stimulating factor treatment.

3 Results

In this study, the skin of all 16 patients was dyed yellow, and in some severe cases was even black (Figs. 1 and 2). This may be due to the mixing and dissolving of yellow powder of 2,4-DNP with the skin and the subcutaneous adipose layer, after consultation with a dermatologist. A larger stained area of the skin with deeper color accompanied more severe symptoms of fever, sweating, chest tightness, and shortness of breath. The effects of physical cooling and symptomatic treatment were not satisfactory; the symptoms of fever and sweating were not relieved, and only ten cases which had less contact had relief from shortness of breath. The two severe patients died of cardiac arrest within 3 h after admission. The fever, sweating, and shortness of breath were relieved after the first HP. The temperatures of six cases became normal within 12 h after the first HP and fever did not return. The remaining eight patients' temperatures were also reduced after the first HP, and rose again after about 8 h, although they were always lower than the highest value before HP. After the third HP, the temperature returned to normal.

On Day 3, after the temperatures of all patients were back to normal, no excessive sweating was

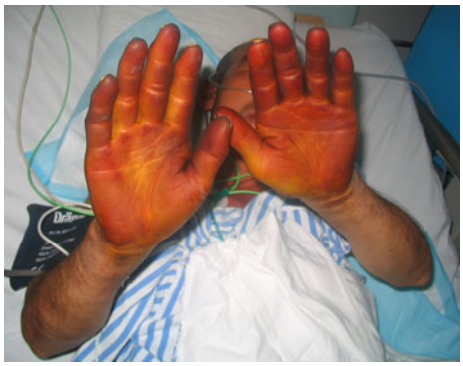

Fig. 1 Brown-tinted hands in cases with acute 2,4-dinitrophenol poisoning

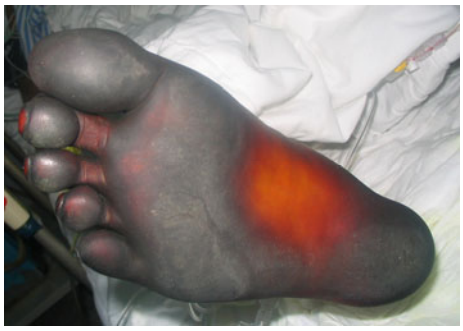

Fig. 2 Affected black planta in severe cases

present and no other evident symptoms were occurring. The contaminated areas of the skin gradually lightened and returned to normal approximately one week later. Hyperlipidemia, especially hypertriglyceridemia, occurred to different degrees in all 14 survivors 7 d after poisoning. The highest level of triglyceridaemia reached 23.5 mmol/L. The level reached a peak at 10–14 d post-exposure, declined afterward, and returned to normal after 3–4 weeks. This phenomenon had no clear correlation with the initial severity of poisoning. No lipid lowering agents were given, only the intake of fats was limited.

Hepatic injury to various degrees appeared in all 14 survivors. The features were presented with an increase of blood glutamic-pyruvic transaminase (GPT) or glutamic-oxalacetic transaminase (GOT) and an elevation of serum bilirubin level. The culmination of hepatic injury ensued within 10 to 20 d post-exposure and became normal about 10 d later. The level of methemoglobinemia was slightly elevated in all the cases at the early stage after poisoning. Furthermore, one case suffered neutropenia, with the lowest level of 1.9×10^9 cells/L. The myelogram showed a granulocyte series associated with a mild toxic change. This patient recovered after taking recombination human granulocyte colony-stimulating factor treatment for 7 d. The two events had no obvious correlation with the initial severity of poisoning.

All 14 survivors recovered and were discharged after four to six weeks of treatment. No evident poisoning sequelae were found at the three-month follow-up.

4 Discussion

2,4-DNP is a protoplasmic poison with high toxicity. It acts directly on metabolism by inducing cellular oxidation and inhibiting phosphorylation, leading to the uncoupling of oxidative phosphorylation (Ray and Peters, 2008). Therefore, the cellular energy in the mitochondria is released directly as heat due to this uncoupling and results in uncontrolled thermogenesis. In the 1930s, some studies showed that administering a small dose of 2,4-DNP stimulates basal metabolism, accelerates gluconeogenesis and glycolysis, and promotes fat mobilization. Therefore, it has historically been used as a diet pill in Europe and America, but was soon banned due to its adverse effects (McFee *et al.*, 2004; Bartlett *et al.*, 2010; Blanck *et al.*, 2007). The profuse perspiration, notable hyperpyrexia, and hyperlipidemia that occurred in our cases might be associated with increased metabolism caused by 2,4-DNP. Furthermore, hepatic injury and neutropenia might be related to its direct toxic effects or systemic inflammatory response syndrome induced by 2,4-DNP.

Most cases concern 2,4-DNP poisoning through the digestive system, following conscious ingestion. However, in this event poisoning through the digestive system was completely excluded. Taking into account that their exposure was in an open environment and all wore standard masks after seeing the yellow powder, we speculated that eleven of them were mainly poisoned through the skin, while the remaining five only having secondary contamination through the skin.

High fever and profuse sweating were symptoms common to all patients, and were related to the degree of exposure; the critically-ill patients died of cardiac arrest in a short time. Because there was no antidote,

clearing toxins from the body and maintaining homeostasis by supportive care were equally important. As a blood purification treatment, we used HP with a styrene/divinylbenzene copolymer. The first choice for blood purification is to absorb toxic substances from blood by a purifier that has a wide adsorption range. This resin can be used to clear poisons that have a large molecular weight, high lipid solubility, and a strong protein-binding ability (Kang *et al.*, 2009; Fertel *et al.*, 2010). When 2,4-DNP enters into the body, it is mainly located in adipose tissue, because of its strong lipid solubility. Therefore, the result of hemodialysis may not be ideal. However, our treatment showed that the typical symptoms of profuse perspiration, hyperpyrexia, dyspnea, and tachypnea were ameliorated and even disappeared, but soon recurred when treatment was ended. On the other hand, this also showed the ability of HP to remove the free 2,4-DNP from plasma. We believe that HP should be listed as the first choice and be administered as soon as possible, but the specific times should be adjusted according to the symptoms, especially body temperature. We also advise that HP could be stopped when the body temperature is restored to normal and maintained for 24 h. Here, we should monitor the procedure carefully because macroporous resin can also absorb normal constituents from the blood such as platelets and glucose.

Clinically, glucocorticoid can inhibit nonspecific inflammation, repress oxygen free-radical generation of neutrophils and macrophages, prevent membranes from releasing proteolytic enzymes, protect hypoxic cells, and alleviate toxic damage to the body (Descatha *et al.*, 2009). Since standard prevention guidelines for 2,4-DNP poisoning are still lacking, dose and usage of glucocorticoid remain uncertain.

In this study, methemoglobin levels increased slightly in all cases at the early stage after poisoning, which indicated that 2,4-DNP can oxidate hemoglobin directly or indirectly and lead to the production of toxic methemoglobin. Therefore, antioxidants such as glutathione, and large doses of vitamins C and E should be used during the treatment. Supportive measures include enhancing the liver protection, maintaining electrolytes and acid-base equilibrium, preventing infection, and providing nutritional supports.

Acute 2,4-DNP poisoning is rare and likely to be misdiagnosed in clinical practice. This accident occurred under a special operation condition with various exposure routes, and taught an important lesson. The rescue effectively underscored the importance of detailed medical history enquiry, close cooperation to the health supervising departments, rapid response, and an active approach to looking for the causes. Furthermore, the uses of HP and glucocorticoid are efficient measures to save the patient's life. Furthermore, medical personnel should be aware of the poison and take protective precautions. Since little information about acute 2,4-DNP poisoning is available, the detailed toxic mechanism and treatment require further investigation.

References

Bartlett, J., Brunner, M., Gough, K., 2010. Deliberate poisoning with dinitrophenol (DNP): an unlicensed weight loss pill. *Emerg. Med. J.*, **27**(2):159-160. [doi:10.1136/emj.2008.069401]

Blanck, H.M., Serdula, M.K., Gillespie, C., Galuska, D.A., Sharpe, P.A., Conway, J.M., Khan, L.K., Ainsworth, B.E., 2007. Use of nonprescription dietary supplements for weight loss is common among Americans. *J. Am. Diet. Assoc.*, **107**(3):441-447. [doi:10.1016/j.jada.2006.12.009]

Descatha, A., Mégarbane, B., Garcia, V., Baud, F., 2009. Delayed immunosuppressive treatment in life-threatening paraquat ingestion: a case report. *J. Med. Toxicol.*, **5**(2):76-79. [doi:10.1007/BF03161092]

Fertel, B.S., Nelson, L.S., Goldfarb, D.S., 2010. Extracorporeal removal techniques for the poisoned patient: a review for the intensivist. *J. Intensive Care Med.*, **25**(3):139-148. [doi:10.1177/0885066609359592]

Kang, M.S., Gil, H.W., Yang, J.O., Lee, E.Y., Hong, S.Y., 2009. Comparison between kidney and hemoperfusion for paraquat elimination. *J. Korean Med. Sci.*, **24**(Suppl. 1):S156-S160. [doi:10.3346/jkms.2009.24.S1.S156]

Kurt, T.L., Anderson, R., Petty, C., Bost, R., Reed, G., Holland, J., 1986. Dinitrophenol in weight loss: the poison centre and public health safety. *Vet. Hum. Toxicol.*, **28**(6):574-575.

McFee, R.B., Caraccio, T.R., McGuigan, M.A., Reynolds, S.A., Bellanger, P., 2004. Dying to be thin: a dinitrophenol related fatality. *Vet. Hum. Toxicol.*, **46**(5):251-254.

Ray, S., Peters, C.A., 2008. Changes in microbiological metabolism under chemical stress. *Chemosphere*, **71**(3):474-483. [doi:10.1016/j.chemosphere.2007.10.026]

Tainter, M.L., Cutting, W.C., Stockton, A.B., 1934. Use of dinitrophenol in nutritional disorders: a critical survey of clinical results. *Am. J. Public Health*, **24**(10):1045-1053. [doi:10.2105/AJPH.24.10.1045]