CASE REPORT

Beware the yellow slimming pill: fatal 2,4-dinitrophenol overdose

Alexander Holborow,¹ Richard M Purnell,² Jenny Frederina Wong³

¹Wales Deanery Postgraduate Medicine, Cardiff University, Cardiff, UK

²Department of Medicine and Cardiology, Abertawe Bro Morgannwg University Health Board, Swansea, UK

³Department of Surgery, Abertawe Bro Morgannwg University Health Board, Swansea, UK

Correspondence to
Dr Alexander Holborow,
aholborow@gmail.com

Accepted 17 March 2016

SUMMARY

An industrial chemical, 2,4-dinitrophenol (DNP), has found use as a weight loss drug. It is extremely toxic in overdose and has a narrow therapeutic window with significant interindividual variability in metabolism. The rise in internet-based sales and distribution of this drug has seen an increased incidence of both accidental and intentional overdose presenting to emergency departments across the UK. No antidote currently exists and overdose is often fatal despite management based on current recommendations. We report a case of intentional overdose of DNP in a young man and discuss the current treatment guidelines. The case highlights the need for an increased awareness among frontline medical staff of the effects of DNP poisoning and questions the need for a more aggressive approach in the management of acute toxicity.

BACKGROUND

The first use of 2,4-dinitrophenol (DNP) in the manufacture of wood preservatives, pesticides, dyes and explosives, was in the early 20th century. At room temperature, it exists as a crystalline substance, slightly soluble in water, with a yellow colour and musty odour and it is still widespread in industrial use.^{1–4} It is extremely toxic in overdose; acute ingestion of 10–20 mg/kg can be fatal.⁵ In the body, DNP acts as an ionophore, dissipating the mitochondrial electrochemical proton gradient that is vital for ATP-synthase function, thereby uncoupling mitochondrial oxidative phosphorylation. This process results in a significant increase in basic metabolic rate, enhanced glycolysis and a marked amplification of thermogenesis even at low doses.¹ Pathological thermogenesis leads to cellular enzyme denaturation, failure of metabolic pathways and, eventually, cell necrosis and organ failure. Observation of these properties led to its popularity as a weight loss drug in the 1930s, before discoveries of its potent toxicity and narrow therapeutic window. Several cases of acute oral exposure to high levels of DNP in humans were reported in the medical literature during the first half of the 20th century, describing a classic symptom complex comprising hyperthermia, sinus tachycardia, tachypnoea and diaphoresis. The presenting symptom is often profuse sweating that may be yellow in colour. Other effects include nausea, vomiting, dizziness and headache. Chronic exposure was found to lead to the formation of 'DNP cataracts', liver failure and agranulocytosis.^{1 2}

These reports led to the banning of DNP from medical prescription in 1938; this legislation saw a subsequent dramatic fall in the incidence of overdose. In recent years, however, there has been a significant increase in reported incidents of toxicity. DNP is now being sold by unregulated online vendors as a weight loss drug. It is promoted aggressively for use among body builders and is known by a number of different names including Dinosan, Sulfo Black, Nitrophen and Chemox.⁶ DNP metabolism has a large interpatient variability and in some individuals, ingestion of even modest doses leads to uncontrollable hyperthermia, haemodynamic compromise, pulmonary oedema, hyperkalaemia and asystole.⁵ Metabolic acidosis is a recognised complication arising due to the rapid increase in the production of pyruvic acid and its subsequent conversion to lactic acid. In a minority of cases, reports of generalised muscle rigidity have been observed, rendering intubation difficult. This effect is believed to arise due to calcium release from the sarcoplasmic reticulum secondary to ATP depletion.^{2 7}

CASE PRESENTATION

A previously healthy 21-year-old man self-presented to hospital 2 h after a deliberate overdose. He had swallowed 17 tablets containing 4250 mg of 2,4-DNP and an unspecified amount of alcohol with suicidal intent. DNP had been supplied by an unregulated internet supplier for weight loss purposes. The patient reported feeling tired, hot and shortness of breath. Initial examination revealed an anxious, overweight man (body mass index 38 kg/m²) with a Glasgow Coma Scale (GCS) of 15. His temperature was normal (36.5°C) but he had a resting tachycardia (126 bpm) and mildly increased respiratory rate (25 bpm). The remainder of the examination was normal. Arterial blood gas analysis was consistent with a mild respiratory alkalosis, presumably resulting from hyperventilation (pH 7.51, PCO₂ 3.7 kPa, PO₂ 14.7 kPa, bicarbonate 27 mmol/L, lactate 2.3 mmol/L). Initial laboratory blood tests, including full blood count, electrolytes, liver function tests and creatine kinase (CK) were all normal and chest radiograph was unremarkable. Intravenous fluid infusion was started and 10 mg oral diazepam was administered following advice from the national poisons unit. Approximately 3 h later, the patient became very agitated and delirious (GCS 12/15). His temperature had increased to 37.9°C and he was heavily diaphoretic, his sweat noted to have a vivid yellow discolouration. Further examination revealed

CrossMark

To cite: Holborow A, Purnell RM, Wong JF. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-214689

worsening tachycardia (157 bpm) and tachypnoea (34 bpm) with a raised blood pressure (197/65 mm Hg). Repeat arterial blood gases showed no significant deterioration.

The patient was attended by the critical care team. Unfortunately, his condition abruptly deteriorated with a sharp rise in temperature to 40.9°C, GCS of 5/15, muscle stiffness and acute pulmonary oedema. He then suffered a cardiac arrest with pulseless electrical activity, approximately 5 h postingestion. Cardiopulmonary resuscitation and advanced life support were started. Endotracheal intubation and ventilation were both impeded by severe global muscular spasm, which continued despite intravenous suxamethonium. A laryngeal mask was therefore inserted and an emergency tracheotomy was then performed. On specialist advice, intralipid was administered intravenously but had no effect. There was no response to cardiopulmonary resuscitation, which was abandoned after 45 min.

INVESTIGATIONS

Autopsy examination revealed severe pulmonary oedema, cardiac enlargement (510 g) linked to obesity and marked congestion of the gastric mucosa. Toxicology confirmed the presence of DNP in blood and urine; the blood level was 23 mg/dL, which is somewhat lower than in previously reported fatal poisonings.

TREATMENT

As no antidote exists, current guidelines recommend giving activated charcoal (50 g) within 1 h of 2,4-DNP ingestion, to reduce gastric absorption.^{5 8} Thereafter, supportive measures focus on the reduction of hyperthermia and intravascular fluid resuscitation. Severe agitation and seizures can be treated with benzodiazepines such as intravenous diazepam 10 mg or lorazepam 4 mg. Fever and diaphoresis should be promptly treated with fluid resuscitation and aggressive cooling measures.^{9 10} Recommended measures include intravenous paracetamol, cooled intravenous fluids, ice packs/bath and cooling blankets.^{8 10 11}

The UK National Poisons Information Service (TOXBASE) advises the use of intravenous dantrolene to manage fever >39°C that does not respond to first line cooling measures.⁸ Dantrolene is the drug of choice for the treatment of malignant hyperthermia (MH), the life-threatening condition rarely provoked by halogenated volatile anaesthetic agents. Dantrolene acts on the ryanodine receptor in the sarcoplasmic reticulum of the muscle cell, inhibiting intracellular calcium release and therefore uncoupling excitation-contraction. Its introduction reduced the mortality of MH from nearly 80% untreated to <10% today.^{10 12}

If hypotension occurs and does not respond to intravenous fluids, intravenous vasopressor and inotropic agents are indicated, in conjunction with invasive monitoring in the intensive care unit.⁸ Renal complications should be identified early. Although haemofiltration continuous venovenous haemofiltration is useful for correcting resistant hyperkalaemia and hyperthermia, it is ineffective in removing 2,4-DNP, which is highly protein bound in vivo. Finally, methaemoglobinemia has been recorded in several case reports—presumably occurring as a result of DNP mediated oxidative stress. If the value exceeds 30%, methemoglobinemia can be treated with supplemental oxygen and methylene blue intravenous infusion, 1–2 mg/kg administered intravenously slowly over 5 min.⁷

DISCUSSION

Over 60 fatalities caused by 2,4-DNP overdose have been reported in the medical literature, the majority occurring in the 1930s. Just two fatalities were reported in the 20th century after 1938, however, more than 12 have occurred since the year 2000, most resulting due to intentional overdose.¹ A recent study recording the incidence of cases of acute 2,4-DNP toxicity presenting to emergency departments in the UK, as recorded by TOXBASE telephone enquiries, reported a significant increase in the period from 2007 to 2013. From just three reported cases for the 5-year period from 2007 to 2011, they observed an increase to 5 in 2012 and 22 in 2013.³ The increasing incidence, high mortality risk and lack of an effective antidote will pose difficult cases for frontline emergency doctors and acute medical physicians.

In the above case, it is striking how the patient's condition deteriorated from one of relative stability to irretrievable hyperpyrexia, heart failure, myotonic spasm and cardiac arrest, despite full supportive measures in a major emergency department. In a review of 62 published cases of deliberate DNP overdose, the average presentation time was 7–8 h postingestion, with average time-to-death at 14 h.¹ This case demonstrates a far more rapid progression: symptom onset occurred at <2 h postingestion, cardiac arrest occurring at just 5 h. This is earlier than any previously reported case.^{1 5} There are no reports of any patient surviving a DNP-related cardiac arrest.^{1 3 13} Evidence of successful management of symptomatic patients in intentional DNP overdose is sparse, but we are aware of a single case report describing a successful outcome.¹¹ In that case, a patient survived an overdose of DNP (600 mg) despite the onset of hyperthermia (39.1°C) and mild rigidity. That patient's life was saved through an aggressive strategy of active cooling, fluid resuscitation, sedation, intubation and ventilation and several doses of intravenous dantrolene, 1 mg/kg. Active cooling was continued for a total of 4 days, until CK levels decreased. It should be noted that the dose ingested was approximately one seventh of that reported here. In summary, DNP is an extremely toxic and dangerous chemical, unfit for human consumption, which is, unfortunately, making its reappearance in emergency medical units in the UK. Deliberate overdose causes horrific and unmistakable effects, with an extremely high mortality rate. In symptomatic patients who have taken a potentially fatal dose, we recommend an aggressive strategy of pre-emptive cooling, fluid resuscitation, early endotracheal intubation, ventilation and

Learning points

- ▶ There is an alarming increase in the incidence of 2,4-dinitrophenol poisoning in the UK, driven by its unregulated distribution via internet sales. Patients are often unaware of the dangers of ingestion.
- ▶ Deterioration can be rapidly fatal. This case demonstrates that from time of symptom onset to cardiac arrest can be considerably quicker than previously reported.
- ▶ Early symptoms may be non-specific, tachycardia and hyperpyrexia may be the only clues.
- ▶ In light of the high mortality, an intensive strategy should be adopted early in symptomatic patients who have taken a potentially lethal dose. This includes active cooling, full supportive measures, dantrolene and early intubation/ventilation on the intensive care unit.

management in an appropriate intensive therapy units/high dependency units setting with full organ support capability. Dantrolene should be considered in cases of hyperthermia not responding to first-line cooling measures and physicians should be cognisant of expected complications including muscle rigidity, rhabdomyolysis, methaemoglobinaemia, hyperkalaemia and renal failure. Even with active treatment, DNP overdose carries a very high risk of mortality due to cardiorespiratory failure.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Grundlingh J, Dargan PI, El-Zanfaly M, *et al.* 4-dinitrophenol (DNP): a weight loss agent with significant acute toxicity and risk of death. *J Med Toxicol* 2011;7:205–12.
- Tewari A, Ali A, O'Donnell J, *et al.* Weight loss and 2,4-dinitrophenol poisoning. *Br J Anaesth* 2009;102:566–7.
- Kamour A, George N, Gwynnette D, *et al.* Increasing frequency of severe clinical toxicity after use of 2,4-dinitrophenol in the UK: a report from The National Poisons Information Service. *Emerg Med J* 2015;32:383–6.
- Lu YQ, Jiang JK, Huang WD. Clinical features and treatment in patients with acute 2,4-dinitrophenol poisoning. *J Zhejiang Univ Sci B* 2011;12:189–92.
- Bradbury S, Vale J. Phenol and related compounds. In: Beteman D, Jefferson R, *et al.*, eds. *Oxford desk reference: toxicology*. Oxford University Press. 2011:258–9.
- Bodybuilding and sports supplements: the facts. NHS Choices. <http://www.nhs.uk/Livewell/Pharmacy/Pages/Body-building-and-sports-supplements-the-dangers.aspx> (accessed 07 Dec 2015).
- Siegmüller C, Narasimhaiah R. 'Fatal 2,4-dinitrophenol poisoning... coming to a hospital near you'. *Emerg Med J* 2010;27:639–40.
- Toxbase. The primary clinical toxicology database of the National Poisons Information Service. <http://www.toxbase.org> (accessed 07 Dec 2015).
- Bartlett J, Brunner M. Deliberate poisoning with dinitrophenol (DNP): an unlicensed weight loss pill. *Emerg Med J* 2010;27:159–60.
- Kumar S, Barker K, Seger D. Dinitrophenol-induced hyperthermia resolving with dantrolene administration. Abstracts of the North American Congress of Clinical Toxicology. *Clin Toxicol* 2002;40:599–673.
- Van Veendendaal A, Baten A, Pickers P. Surviving a life-threatening 2,4-DNP intoxication: 'Almost dying to be thin'. *Neth J Med* 2011;69:154.
- Krause T, Gerbershagen MU, Fiege M, *et al.* Dantrolene—a review of its pharmacology, therapeutic use and new developments. *Anaesthesia* 2004;59:364–73.
- Yen M, Ewald MB. Toxicity of weight loss agents. *J Med Toxicol* 2012;8:145–52.

Copyright 2016 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow