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Case Report

Role of dantrolene in dinitrophenol (DNP) overdose: A continuing question?☆,☆☆,☆☆☆

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ABSTRACT

Background: 2,4-Dinitrophenol (DNP) is a known uncoupler of oxidative phosphorylation that clinically results in hyperthermia, tachycardia, tachypnea, and metabolic acidosis. Overdoses of DNP are often fatal and there is no specific reversal therapy. Dantrolene interferes with calcium release in skeletal muscle and is traditionally used to treat malignant hyperthermia. There has been limited published data on its use in DNP toxicity. We present two cases of DNP toxicity that were treated with dantrolene.

Case 1: A 22-year-old male presented following an overdose of his bodybuilding supplements including DNP. He became altered, tachycardic, and hyperthermic to 40.0C. He required intubation and aggressive cooling. He received multiple doses of dantrolene over the initial 36 h with resolution of his hyperthermia. He was extubated and discharged home on hospital day 6.

Case 2: A 20-year-old male presented following a staggered ingestion of DNP. He was tachypneic and tachycardic on arrival. He became hyperthermic to 40.2C and required intubation. He underwent aggressive cooling and received 200 mg of IV dantrolene. His temperature normalized, however, he expired 4 h after ED arrival.

Conclusion: DNP toxicity has limited treatment options. Dantrolene may ameliorate the hypermetabolic state in DNP toxicity by lessening excitation-contraction coupling in muscle cells and improving the associated hyperthermia. Our cases demonstrate the hyperthermia reducing effects of dantrolene in DNP toxicity and contribute to the existing literature on this topic. Being aware of the possible use of dantrolene to treat the associated hyperthermia could assist emergency physicians in the treatment of DNP toxicity.

1. Introduction

2,4-Dinitrophenol (DNP) has been used historically as a weight loss agent until it was banned by the US Food and Drug Administration in 1938 due to its toxicity and associated deaths [1-4]. Recently, the medical community has seen increased DNP poisoning secondary to its availability online [1,4]. DNP causes uncoupling of oxidative phosphorylation and inhibition of ATP formation resulting in an increased metabolic rate and hyperthermia, leading to alterations in cellular functioning [1,2,4,5]. DNP toxicity presents with tachycardia, tachypnea, hyperthermia, and metabolic acidosis. Deaths are related to an increased adrenergic state resulting in hyperthermia and cardiac arrest [1,2,4,5].

Treatment of DNP toxicity is primarily supportive. Dantrolene has been suggested as a possible treatment for DNP associated hyperthermia [1-3] with a few case reports of its use [6-8]. We present two cases of dantrolene use in DNP toxicity with improvement in the associated hyperthermia.

2. Case 1

A 22-year-old male presented to the emergency department (ED) after being found confused. He reported taking a double dose of his bodybuilding supplements including: hydroxyzine, creatine, taurine, levothyroxine, and DNP. He was confused, diaphoretic, and tremulous with initial vital signs of HR 113 beats per minute, BP 112/71 mm Hg, and temperature 37.1C. Laboratory testing demonstrated: creatinine 2.11 mmol/L, glucose 499 mg/dL, and creatine phosphokinase 456 units/L. Toxicology testing was negative for ethanol, acetaminophen,

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aspirin, amphetamines, and cocaine. Eight hours after arrival, he became febrile 38.6C and required intubation. Following intubation, 180 mg of dantrolene was administered intravenously. Three hours later, his temperature reached a maximum of 40.0C. He received five additional doses of dantrolene over the next 36 h for a total of 780 mg (9.4 mg/kg). Non-invasive cooling was started approximately 2.5 h after initial dosing. His hyperthermia resolved approximately 5.5 h after the initial dantrolene dose and did not recur. He was extubated on hospital day (HD) 4 and discharged on HD 6.

3. Case 2

A 20-year-old-male with a history of depression presented to the ED 5 h after a staggered ingestion of 8 tablets of DNP earlier that day, last dose 3 h prior to arrival. Vital signs upon arrival were: BP 138/96 mm Hg, HR 148 beats per minute, RR 26 breaths per minute, oxygen saturation of 96% on room air and temperature of 37.7C. Physical exam demonstrated diaphoresis, tachypnea and tachycardia. Laboratory testing demonstrated: creatinine 1.17 mmol/L, creatine phosphokinase 146 units/L and negative acetaminophen, salicylate, and ethanol levels. An hour after arrival, temperature reached a peak of 40.2C. Aggressive cooling was started and he was intubated. 200 mg of IV dantrolene was administered. A repeat temperature 25 min after dantrolene administration was 37.0C. Unfortunately, the patient expired 1 h after dantrolene administration and approximately 4 h after ED arrival.

4. Discussion

Current treatment of DNP toxicity is limited. Standard of care is aggressive supportive care, as there is no antidote. Activated charcoal can be considered for patients with normal mentation presenting within 1 h of ingestion [1]. Treatment focuses on aggressive fluid resuscitation and cooling with ice packs, cooling blankets, and cold intravenous fluids. Airway management and monitoring of electrolytes and renal function are often necessary. Benzodiazepines are recommended for agitation or seizure activity [1,2]. Hemodialysis is not recommended for DNP toxicity; however, it may be considered for correction of acid-base abnormalities.

Dantrolene is traditionally used for malignant hyperthermia and acts to limit calcium release from the sarcoplasmic reticulum, decreasing muscular contractions and limiting further heat production [1,2,9]. Heat production in DNP toxicity is secondary to uncoupling of oxidative phosphorylation, which inhibits ATP production [1,2,9]. Reduced availability of ATP alters calcium transport, causing increased intracellular calcium, which may lead to increased muscle contractions and heat production [2,3,9,10]. Dantrolene has been used successfully in case reports for the treatment of DNP toxicity [6-8], the proposed mechanism being decreased intracellular calcium [3,9,10].

Current literature consists of two abstracts and one letter to the editor reporting successful resuscitation of patients with dantrolene in DNP poisoning [6-8]. All three cases reported decrease in temperatures after dantrolene, however, two of the cases also performed aggressive cooling techniques [6-8]. While only one of our cases survived, both of our cases suggest improvement in DNP associated hyperthermia following dantrolene administration. The reduction of hyperthermia in our cases provides additional experience for the use of dantrolene in DNP poisoning.

5. Conclusion

DNP causes uncoupling of oxidative phosphorylation, leading to hyperthermia and cardiovascular collapse. DNP toxicity has a high fatality rate with limited available therapies. Dantrolene may ameliorate the hypermetabolic state by lessening excitation-contraction coupling in muscle cells and improving the associated hyperthermia. Further study and experience are needed to define the exact role of dantrolene in the context of DNP poisoning.

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