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2, 4 - Dinitrophenol Toxicity-Bound Mortality in Patients Doing Bodybuilding

Medical Science

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ABSTRACT

2,4-Dinitrophenol (DNP) intoxication is a condition that may result in mortality together with uncontrolled hypothermia and epidemic muscle rigidity. In excessive doses, hyperthermia, tachycardia, excessive sweating, tachypnea, acute renal damage, confusion, agitation, convulsion, and coma may be observed. DNP therapeutic index is a narrow agent. In acute and suicidal exposure, the oral lethal dose changes between 2,8 and 5 gr, and the average has been reported as 4,3 mg/kg. The dose taken orally by our patient who is known to be a sportsman doing body-building exercises is below the lethal dose of 1,8 gr. It must be taken into consideration that a patient can be lost even if the dose is below the lethal dose and adequate support treatment is applied.

INTRODUCTION

2,4-Dinitrophenol (DNP) is a metabolic toxin affecting mitochondrial oxidative phosphorylation through separation and leading to uncontrolled hyperthermia (1). It is used as a component of pesticides as well as for production of insecticides and explosives. It began to be used in patients for losing weight in 1930s in the USA. However, it was later banned due to its severe side effects (2,3). DNP was labelled as "not appropriate for human use" by the Food and Drug Administration in the USA in 1938 and by the Food Agency in England in 2003 (4).

There are 62 mortality cases published to date due to accidental or suicidal DNP intake. The broadest study was published in 1919 and 36 deaths developing after professional exposures in Paris were reported. In the recent 10 years (2001-2010), the number of deaths after exposure to DNP is 12 (4).

Today, DNP is sold over the internet under such names as 'DNP', 'Dinosan', 'Dnoc', 'Solfo Black', 'Nitrophen', 'Aldifen' and 'Chemox', 'NitroKlenup' and 'Caswell No. 392' (4,5). DNP stimulates the oxidative metabolism strongly and rapidly in addition to oxygen consumption, and when it is taken orally at a 3 mg/kg dose, it increases the basal metabolism by 50% (6). In addition to being market through the internet as "the drug enabling to lose weight safely", it is particularly targeted toward body-builders and suggested to be used for losing fat by protecting muscles (4). In this study, we aimed to present the patient doing body-building sport and developing death due to DNP use.

CASE

The 30-year-old male patient weighing 80 kg was admitted to the emergency ward with a history of drug use. It was learned that the patient who showed no symptoms of a side disease was a sportsman, did body-building exercises and used such drugs as DNP, growth hormone and clamiterol. We were informed that the patient took 9 DNP capsules, though he takes 4 capsules every day, and then applied to a hospital with complaints of fever, tachycardia, sweating and troubled respiration. In the hospital providing initial care, a nasogastric catheter was inserted to the patient and stomach lavage was applied but he was transferred to our hospital since the heart pulse rate (HPR) was high (130-140 pulse/min) and leucocyte and metabolic alkalosis were detected.

The patient being examined in the emergency service was conscious, cooperated, oriented, pupillary bilateral isochoric and midriatic; and the Glaskow Coma Scale (GCS) was 15/15. In the physical examination conducted, the following values were detected; HPR: 136 pulse/min., Tension Arterial (TA): 150/80 mmHg, Fever: 37,4 $^{0C.}$ Respiration Rate: 36/min. The noise of lungs was normal. There were no pathological findings in the posteroanterior lung graph (Figure 1). There was no additional sound or hissing in the cardiovascular system examination. In the ECG, there was sinus tachycardia, and there was minimal ST depression in V5-V6 (Figure 2). In the abdominal examination, the abdomen was stretched and there was no defense or rebound. The blood biochemical values in the laboratory findings were as follows: glucose:184mg/dL (ref:74-106), urea:83.5 mg/dL (ref:20-50), creatine:2.16 mg/dL (ref:0.7-1.3), AST:53 U/L (ref:1-40), ALT:49 U/L (ref:7-49), LDH:350U/L (ref:120-246), creatine kinase:1049 U/L (ref:32-294), potassium:5.6 mmol/L (ref:3.5-5.5), total protein:8.3 g/dL (ref:5.7-8.2), albumin:5.2 g/dL (ref:3.2-4.8). The other biochemical values were within normal limitations. The leucocyte: 18.760/mm3 (ref:3.2-9.7), and the other values were within normal limits. There were proteinuria and hematuria in the full urine examination. Blood gas values were within normal limitations.

The patient received aggressive liquid resuscitation in the emergency service and intravenous (iv) diltiazem 25 mg was applied for tachycardia. Considering the fact that the patient might have hyperthyroidism crisis, iv methylprednisolone 250 mg and 50 mg ranitidine were applied and then the blood sample was sent for thyroid function tests. As antipyretic, 1000 mg of paracetamol was applied intravenously. Since there was an increase in the levels of urea and creatine together with hematuria in liver function tests, the case was evaluated by the internal diseases clinic. With the pre-diagnosis of drug intoxication and acute renal fail-

ure due to the drug, follow-up in the internal diseases clinic was deemed appropriate. While the patient was followed up in the internal diseases clinic, the patient was evaluated by the anesthesia and reanimation clinic when the respiration problem increased at the end of the 1st hour and follow-up of the patient in the intensive care unit was deemed appropriate. When the patient was taken to the intensive care unit, the values were as follows; TA: 105/63 mmHg, HPR:120 pulse/min., Fever: 38,2 0C, Respiration rate: 32/min, GCS 15/15. In the physical examination, a common rigidity began though slightly in the locomotor system. The patient, whose rigidity progressively increased in the locomotor system was intubated through orothraceal access receiving iv midazolam 5 mg and rocuronium 40 mg after 45 minutes following his acceptance to the intensive care unit when the respiration problem increased excessively and confusion developed. However, the muscle rigidity continued to increase. At this point, the fever of the patient was measured to be 42,9 0C. Cold application was made with ice and iv 1000 mg paracetamol was applied. Due to the rigidity in the chest muscles, effective ventilation could not be obtained with the mechanic ventilator. When the patient developed cardiopulmonary arrest, Cardio Pulmonary Resuscitation (CPR) was applied. Due to intensive rigidity, an effective CPR couldn't be applied; however, active CPR application was continued to be applied for 1 hour. Since no response could be obtained, the patient was accepted as exitus.

DISCUSSION

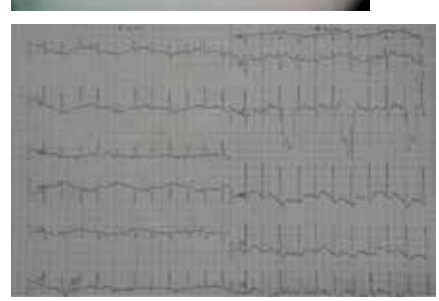
Although a dermal or respiratory exposure to DNP was reported, oral exposure for therapeutic or suicidal purposes is the most common etiology (4,7). DNP is mostly in 100-200 mg capsule form on the market; it is suggested that it must be used as combined with thyroxin or an anabolic steroid. It is suggested in typical use to begin with 1x1 capsule for the first few days and to use 400 mg/day at the most on the following days (4). The agent whose therapeutic index is narrow is highly dangerous in case of an excessive dose intake. The oral lethal dose in acute and suicidal exposure ranges between 2,8 and 5 gr, and the average was reported to be 4,3 mg/kg. In addition, a single female patient was reported to be exposed to a high amount of dose such as 2,4 gr but not develop any complications (4). Our patient took 9 capsules of 200 mg through oral access for body-building purposes. It is below the 1,8 gr lethal dose. However, the patient had a history of chronic use of the drug as 4 capsule/day for 6 months. Though not currently present in the literature, we are of the opinion that chronic use has a contribution to mortality.

The symptoms observed in overdose intake of phenol-based products such as DNP are reported to include common neurologic effects such as hyperthermia, tachycardia, excessive sweating, tachypnea, acute tubular necrosis and acute renal damage, confusion, agitation, convulsion and coma (4). The symptoms observed in our patient were in compliance with the literature. No neurologic finding was observed until the patient was accepted to the intensive care unit. The symptoms started an hour after drug intake. The period between drug intake and death was 15 hours. In the literature, the beginning of the symptoms after DNP intake is between the first 30-180 min. and the mortality period is 14 hours on average. It was reported at that fever, heart rate and heart pressure rates were not together at the beginning but if not treated, can progress fatally as a result of tachycardia, tachypnea, shock, confusion, convulsions, cardiovascular collapse and pulseless electrical activity (4). However, in our patient, there was a history of tachycardia beginning with fever, sweating and respiratory problems. It was reported that mortality is generally secondary to cardiovascular collapse; general rigidity may develop rapidly within a few minutes after death and if this deep muscle rigidity is observed before death, there may be difficulty in application of mechanical ventilation (8). In our patient, although there was tachycardia, no cardiovascular collapse occurred. The reason for death was respiratory problem due to common muscle rigidity; inability to provide mechanical ventilation due to muscle rigidity after intubation and inability to apply an effective CPR due to the same reason.

There is no specific antidote for DNP. Early diagnosis is important (9). Patients who have overdosed must be under close follow-up for 12 hours and their body warmth, heart rate and oxygen saturation must be carefully monitored. A patient progressing asymptomatically for 10 hours after acute overdose was reported (1). Oral active coal application in DNP intoxication is suggested to be applied within the first 1 hour after the digestive track is taken (4). When our patient came to the emergency service, 4 hours had passed after the drug intake. Aggressive liquid resuscitation must be applied in toxication resulting from DNP (4). Attacks and serious agitation must be controlled with benzodiazepines. If an agitation or attack cannot be controlled, intubation and ventilation must be considered. In case of hyperthermia, external cooling precautions, ice bath and cooling blankets must be used (4). Early period dantrolen use is suggested for control of the heavy hyperthermic case (8). However, dantrolen was used successfully only in one patient (4). Our patient also received intensive care treatment, aggressive liquid treatment and treatment suggested for hyperthermia as of the moment he was taken to the emergency service. Since there was no dantrolen in our hospital, it could not be applied.

It has been demonstrated in experiments on rabbits that when DNP concentration increases in the blood, potassium is accumulated in the kidney (4). Hyperpotecemia was also present in our patient's first blood examinations (P:5,6). Together with overdose, continuous veno-venous hemofiltration use has been suggested in hyperkalemia and hyperthermia methods (4,8). He et al. reported that early hemoperfusion in acute DNP overdose reduces the mortality rate (10). However we didn't have time to apply hemofiltration since the respiratory problem increased progressively and the muscle rigidity developed rapidly after acceptance to the intensive care unit.

As a result, this study presents the first patient demonstrating exitus after 1,8 gr DNP intake in the literature. It must be taken into consideration that patients can be lost even if the taken dose is below the lethal dose and adequate support treatments are applied.



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