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CASE REPORT

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Acute Intoxication by Endosulfan: Any Role of N-Acetylcysteine Therapy?

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Abstract: Reactive oxygen species may play a role in the mediation of acetaminophen (APAP) hepatotoxicity. N-acetylcysteine (NAC) is the standard therapy for treatment of the APAP overdose patient. The suspected mechanism of hepatic injury appears to be similar to that of APAP and the empiric use of NAC may be justified, especially in significant endosulfan poisoning.

An 18-year-old male presented to the emergency department because of unconsciousness and seizure that developed after acute intentional ingestion of endosulfan. Severe diaphoresis was noted and he had a Glasgow Coma Score of 7 (E1M4V2). Within 8 hours of his arrival in the emergency department, progressive elevation of transaminases was detected and NAC was administered via the intravenous route. Within the next 5 days the serum levels of transaminases returned to normal and he was discharged in good condition.

We suggest that in patients with endosulfan poisoning who have primarily hepatotoxicity, NAC administration might be considered. NAC therapy was well tolerated and there were no serious adverse effects. Nevertheless, further data are required to demonstrate the efficacy of NAC therapy in endosulfan poisoning, and guidelines for dosing regimens have to be provided.

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Key Words: Endosulfan, n-acetylcysteine

Akut Endosulfan Zehirlenmelerinin Tedavisinde N-Asetil Sistein Uygulanmalı mı ?

Özet: Parasetamol zehirlenmelerinde karaciğer hasarı gelişiminde reaktif oksijen bileşenleri önemli rol oynamaktadırlar. Parasetamol yüksek doz alımlarında standart tedavi, N-asetil sistein (NAC) uygulamasıdır. Ciddi endosulfan zehirlenmelerinde, hepatik hasar benzer mekanizma ile geliştiğinden dolayı, deneysel NAC kullanımı tedavide yararlı olabileceğinden göz önünde bulundurulmalıdır.

18 yaşında genç bir erkek, intihar amaçlı endosulfan alımı sonrasında, acil servise bilinç bozukluğu ve nöbet geçirme şikayeti ile getirildi. Hastanın aşırı terli ve Glasgov koma skorunun E1M4V2 olduğu tespit edildi. Hastanın acil servis takibinde, 8 saat içinde karaciğer enzimlerinde belirgin artış olması üzerine intavenöz NAC uygulandı. 5 gün içerisinde karaciğer transaminaz seviyeleri gerileyen ve genel durumu düzelen hasta sağlıklı olarak taburcu edildi.

Endosulfan zehirlenmelerinde ciddi karaciğer hasarı şüphesi varlığında NAC uygulaması yararlı olabileceğinden tedavi amacıyla denenebilir. NAC tedavisi iyi tolere edilmektedir ve herhangi bir yan etkisi izlenmemiştir. Bununla birlikte endosulfan zehirlenmelerinde NAC tedavisinin yararını ve doz etkinliğini belirlemek amacıyla daha fazla veriye ihtiyaç vardır.

Anahtar Sözcükler: Endosulfan, n-asetil sistein

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Introduction

Endosulfan is a highly toxic organochlorine insecticide that produces well-known neurological symptoms of tonic-clonic convulsions, headache, dizziness and ataxia, but can also cause gastrointestinal symptoms, severe myocardial insufficiency, metabolic disturbances, and cerebral and pulmonary edema (1). Exposure to higher polychlorinated compounds resulted in mortality, liver damage and degeneration of the kidneys. Results from the literature data indicate that hepatotoxicity of polychlorinated compounds manifests itself in hepatomegaly and in liver focal fatty degeneration or liver fibrosis (2). Free radicals play an important role in the toxicity of pesticides (3). Recent data have indicated that reactive oxygen species may play a role in the mediation of

acetaminophen (APAP) hepatotoxicity. N-acetylcysteine (NAC) is the standard therapy for treatment of the APAP overdose patient (4). The suspected mechanism of hepatic injury appears to be similar to that of acetaminophen, and thus the empiric use of NAC may be justified because of the theoretical benefit of a protective effect from oxidative stress in the liver, especially in significant endosulfan poisoning (5).

Case Report

An 18-year-old male presented to the Emergency Department (ED) due to unconsciousness and seizure developing after an acute suicidal ingestion of three teaspoons (approximately 100 g) of insecticide megasulphan powder. He was found by his family on the bedroom floor, 1 hour before presentation. He was admitted to our ED approximately 2 hours after ingestion. On physical examination, the patient's blood pressure was 140/80 mmHg, pulse 150 beats/min, respiratory rate 22 breaths/min, temperature 39.9°C and pulse oximetry 95%. His Glasgow Coma Score was 7 (E1M4V2) and he had generalized tonic-clonic convulsions. The rest of the physical examination was unremarkable. An initial electrocardiogram showed sinus tachycardia without signs of ischemia. Chest radiograph revealed no abnormality. The patient was endotracheally intubated for airway protection. Midazolam (Dormicum®) 5 mg/h intravenous (IV) was administered for prophylaxis of seizure and sedation. After orogastric lavage with suction, multiple doses of activated charcoal 1 g/kg and cholestyramine 9 g were administered via the orogastric tube. Initial laboratory values revealed a white blood cell count of 29.3 U/L, hemoglobin level 17.4 g/dl, hematocrit 50.2%, platelet count 493 K/UL, Na^+ 145 mmol/L, K^+ 4.6 mmol/L, creatinine kinase (CK) 7720 U/L (normal reference range: 26-308 U/L), CK-MB 130 IU/L (normal reference range: 7-25 U/L), cardiac troponin-I (cTnI) 0.182 ng/ml on presentation (normal reference range: 0.00-0.03 ng/ml), BUN 23 mg/dl, and creatinine 1.0 mg/dl. His AST and ALT (normal reference range: 0-40 U/L) changed over time (Table). Within 8 hours of his arrival in the ED, progressive elevation in serum levels of transaminases was detected and NAC was administered at the 10th hour of ingestion via IV at 140 mg/kg loading dose over 15 minutes, followed by 50 mg/kg infused over 4 hours, followed by 100 mg/kg over 16 hours after maintenance. A brain computed tomography scan was obtained and revealed mild edema. Within the next 5 days, the patient's neurological status improved. Since the serum levels of transaminases returned to normal and the patient's mental status improved sufficiently to be extubated on the 5^{th} day after first presentation, the patient was admitted to the psychiatry clinic.

Table. Serum levels of transaminases.

	1 hr	6 hrs	18 hrs	24 hrs	48 hrs
AST	111	454	700	603	296
ALT	114	91	178	171	125

AST: aspartate aminotransferase;
ALT: alanine aminotransferase.

Discussion

Extensive use of very hazardous pesticides continues in Central America, as do poisonings, with organophosphates, carbamates, endosulfan and paraquat as the main causative agents. There is a gross underreporting and underdetection of acute health effects (6).

A number of studies have provided evidence for the capacity of organochlorine pesticides to induce oxidative stress in different organs of mammals. One reported the oxidant stress-inducing effects of endosulfan, a chlorinated hydrocarbon insecticide, with an increase of lipid peroxidation and a significant alteration in glutathione redox cycle in cerebral and hepatic tissues of rats (7). Endosulfan augmented production of superoxide and hydrogen peroxide and decreased the levels of certain antioxidant enzymes. Exposure to endosulfan caused apoptosis and necrotic cell death. To minimize oxidative damage to cellular components, cells have adaptive mechanisms to increase antioxidant defenses (8). NAC, a cysteine analogue, can act as an antioxidant by directly reducing free radicals and oxidants such as $OH^{\cdot}$ and H_2O_2 and is a chemoprotective agent against the toxic effects of many compounds (7) Favorable outcomes following the use of NAC have been reported in cases of carbon tetrachloride poisonings (9). NAC has been shown to be effective in treating endosulfan poisoning in a limited number of animal and human cases (7,10). Koca et al. (10) reported that their first case, who was given NAC at the 30^{th} hour of ingestion of endosulfan, died at the 155^{th} hour. Their second case received NAC 16 hours after

ingestion. He began to recover at the 80th hour and was discharged on the 7th day, but the amount of toxin ingested was unknown. Early NAC treatment may be beneficial in overall morbidity and mortality. It may be helpful in the more rapid decrease of elevated serum transaminases than traditional treatment modality (7). Rapid decrease in serum levels of transaminases in our case may be attributed to the protective effect in the liver from oxidative stress with NAC treatment in the early period. We speculate that this treatment may be beneficial. There is really no evidence of efficacy in this case - just the observation of the recovery of liver function tests. Although the presented isolated case has limited value, it is certainly of interest whether or not NAC actually helps in hepatic injury from endosulfan insecticide poisoning.

In conclusion, we suggest that in patients with endosulfan poisoning who have mainly hepatotoxicity, NAC administration might be considered. NAC therapy was well tolerated and there were no serious adverse effects. Nevertheless, further data are required to demonstrate the efficacy of NAC therapy in endosulfan poisoning, and guidelines for dosing regimens have to be provided.

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