Case Report

Revisiting Endosulfan

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Abstract

Endosulfan toxicity could precipitate gargantuan jeopardy and may result in irreversible and fatal damage. The spectrum of involvement may range from mild nausea, vomiting, and anxiety to intractable seizures and multiorgan damage resulting in death. We report a case of endosulfan poisoning complicated by multi-organ dysfunction, cardiac arrest, and death.

Keywords: Endosulfan, multi-organ failure, seizures

Introduction

Endosulfan (hexachloro-hexahydro-methano-benzodioxathiepinoxide) is an organochlorine insecticide and acaricide. All routes of exposure can be hazardous (stomach, lungs, skin). India is currently touted the world's largest user and producer of endosulfan.[1] With a plethora of toxic manifestations, endosulfan can trigger a progressive unremitting down-hill course especially if complicated by multi-organ failure. We discuss one such case of fatal endosulfan poisoning and review the literature.

Case Report

A 17-year-old female presented with history of ingestion of about 35 ml of an insecticide (containing endosulfan 35% EC) 4 hours ago following which she developed continuous involuntary jerky movements and associated up-rolling of eyes and frothing from the mouth. She was taken to the local hospital where she was given benzodiazepines and phenytoin, intubated and mechanically ventilated and rushed to our center for further care. Glasgow coma scale was 3 on arrival. Activated charcoal was given and the prior gastric lavage sample was sent for analysis. The patient continued to seize and midazolam and lorazepam infusions were given with no benefit followed by phenobarbital and propofol. Seizures persisted and Levetiracetam was tried but in vain. Hypotension was noted and inotropic support added.

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Blood gas analysis showed high anion gap metabolic acidosis. ECG showed sinus tachycardia with ST depressions in II, III, AVF, and V4-V6. 2D Echo showed paradoxical motion of intraventricular septum with dilated right atrium and ventricle without PAH. Labs showed TWBC-44,800 which subsided over the next few days. S creatinine increased from 1.75 to 6.06 mg/dL and SGPT from 19 to 473 IU/L. S-Ca- 7.3 mg/dl; S Mg-3.1 mg/dL; LLDH- 3347 U/L. The peak serum concentration of endosulfan was 1.82 mg/L about 23 hours after ingestion. Supportive treatment with antibiotics, hemodialysis and hydration continued. CT brain showed evidence of cerebral edema [Figure 1]. Electroencephalogram (EEG) was suggestive

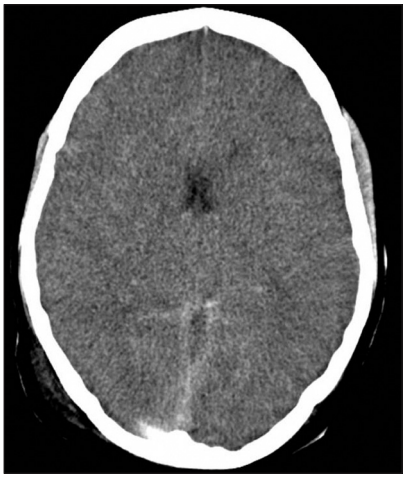

Figure 1: CT brain showing generalized hypodensity with near complete obliteration of ventricular systems, basal cisterns, and sulcal spaces suggesting cerebral edema

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of severe anoxic/ischemic encephalopathy. Chest X-ray (CXR) showed mild ground glassing on the right. Multi-organ failure was noted with acute kidney injury, hepatitis, acute lung injury, myocardial depression, and encephalopathy. Her seizures were unrelenting and she developed multiple episodes of bradycardia and cardiac arrest before finally succumbing to death.

Discussion

Central nervous system (CNS) hyper-stimulation (with little or no peripheral component) is the predominant toxicological effect of endosulfan mediated by inhibition of calmodulin-dependent Ca- and Mg-ATPase and antagonism of chloride ion transport in gamma-aminobutyric acid receptor/ionophore complex which releases the synaptic inhibition on neurons.[2] Continued CNS toxicity can be explained by its property of being both a substrate and inhibitor to the cellular efflux transporter p-glycoprotein (p-gp), which allows endosulfan to enter and remain in the CNS (lipophilicity). A report from Jabalpur (Madhya Pradesh, India) showed that a community spanning all age groups had convulsive illness of varying severity over a period of 3 weeks which up on investigation was traced to unintentional poisoning from storing drinking water in empty endosulfan cans, its percolation in to food etc.[3] Reduced acetyl cholinesterase activity, positive caspase-3 reaction, and histopathological jeopardy in cerebrum and cerebellum characterized by endosulfan toxicity were shown to be ameliorated by Vitamin C.[4]

Endosulfan is also an endocrine disruptor and carcinogen and is proven to induce oxidative stress, increase lipid peroxidation, and to significantly alter glutathione redox cycle. In animal models, hepatomegaly, sinusoidal dilation, pyknotic nuclei, cytoplasmic degranulation, and various nuclear aberrations were observed in the liver and the kidneys showed chronic glomerulonephritis, glomerulosclerosis, edema, and glomerular deposits.[5] Hemorrhages, degeneration, and slight gliosis can be seen in the brain. Decreased Red Blood Cells (RBC) and hemoglobin with increased White Blood Cells (WBC) (significantly raised basophils and monocytes seen in our patient), hyperglycemia, raised Lactate Dehydrogenase (LDH), Creatine kinase (CK) and CK-MB levels can also be seen.

The symptoms usually begin with in the first hour (depending on the factors affecting absorption). Common symptoms are anxiety, nausea and vomiting, abdominal discomfort, hyperaesthesia of the mouth and face, tongue and extremities, headaches, agitation, hyperactivity, incoordination, confusion, dizziness, myoclonus, and seizures.[6] Generalized tonic-clonic seizures comprise more than 80% although focal seizures are not uncommon. Status epilepticus (SE) has the potential danger of causing asphyxia.

Hypoxia (from SE/aspiration/respiratory failure secondary to pneumonia) can be combated by mechanical ventilation. Metabolic acidosis is an important accompaniment probably relating to lactic acidosis from seizures. Hypotension and ECG abnormalities are commonly reported and may revert with prompt supportive therapy.

Multi-organ failure may involve liver (hepatitis with raised transaminases, and hyperbilirubinemia), kidney (azotemia), brain (encephalopathy, seizures), heart (rhythm disturbances, myocardial depression), and lung (ARDS, pneumonia) as depicted in our patient. Rhabdomyolysis, acute kidney injury, disseminated intravascular coagulation, thrombi in the pulmonary arteries and aorta, and cardiogenic shock point toward a more severe end of the spectrum.

Seizure, Glasgow coma scale score, systolic blood pressure, bicarbonate level, need for respiratory support, pulse rate, respiratory rate, pH (mainly arterial), base excess, and duration of seizure correlate with mortality (fatality rate of 54.1%).[7] Amount of endosulfan ingested (>35 g) is an independent variable predicting mortality.[8] Refractory SE is an important and common cause of death with multi-organ failure contributing a fair share. In a case series on 34 patients of organochlorine poisoning (16 of them on endosulfan) mechanical ventilation was required in 69% and vasoactive agents in 19% with in-hospital mortality of 19%.[9]

High-resolution gas chromatography can detect endosulfan in the serum, tissue, and urine. Brain imaging may reveal cerebral edema (as in our case) and Magnetic Resonance Imaging (MRI) may delineate the ischemia afflicted basal ganglia, occipital and prefrontal cortex.

Hemoperfusion has not shown any benefit in clearing the drug. Benzodiazapines and phenobarbital are recommended to control seizures (endosulfan's action being Gamma-aminobutyric acid (GABA) mediated and hence phenytoin being less efficacious). Propofol, valproic acid, topiramate, and levetiracetam may also be tried.

Endosulfan poisoning is a devastating catastrophe with very high mortality. As there is no antidote available, aggressive supportive treatment remains the mainstay of management.

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