TOXICOLOGY REVIEW

Organochlorine (Endosulfan) Poisoning

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Endosulfan (C9H6Cl6O3S) is a highly toxic organochlorine which belongs to cyclodienes group widely used in agriculture (1, 2). It induces T-cell apoptosis, mitochondrial dysfunction, oxidative stress (3, 4) and lipid peroxidation (5, 6).The predominant toxicological effect is over-stimulation of the central nervous system (CNS) in the form of seizures. Hypoglycemia or Hypergycemia, cerebral edema, metabolic abnormalities, & multiple organ toxicities involving brain, liver, blood & kidney are common with this poison (7-10). Their exist dilemmas among emergency clinicians and intensive care units team, difference of opinion & lack of consensus in treatment guidelines, of this relatively uncommon poisoning which often lead to permanent lifelong morbidity or even mortality. No specific antidote exists. Role of PAM is controversial in organochlorine poisoning.

No well established neuro-protective drugs against neurodegenerative changes exist. There are few isolated case reports (1, 7-9) and case series of 23 cases (10) of accidental and suicidal poisoning with ES available during scan of literature. Thus, there remains scanty data on ES poisoning and its treatment. Moreover, the unrestricted use of these compounds in developing countries have resulted in the death of large number of humans, which makes current write-up important clinically, as the poisoning with such poison can be challenge for treating clinicians here also in our setup.

Various symptoms, signs & biochemical parameters reported in humans after ES intoxication in literature include: abdominal pain, nausea, vomiting, foamy oral fluid, chest pain, sinus tachycardia, hypertension, miosis (which may be followed by mydriasis), hypoglycemia, elevated activity of liver enzymes, hyperthermia, rhabdomyolysis, acute interstitial nephritis, acute tubular necrosis , metabolic acidosis combined with a elevated anion gap , hyperlactatemia, respiratory distress, respiratory arrest, tremor, ataxia, convulsions, unconsciousness, normal level of serum pseudocholinesterase activity , leukocytosis and thrombocytopenia (7-10).

The predominant toxicological effect is over-stimulation of the CNS. One of the case series reported that seizures began within one hour after ingestion in (52.2%), in the second hour in (39.1%), and in the third hour in (8.7%). Seizure are generalized tonic-clonic in (84.2 %) and focal seizures in (15.8%) (10). The most likely reason for continuous sustained status epilepticus could be hypoglycemia, cerebral edema, hypoxic injury & metabolic abnormalities, particularly causing metabolic acidosis and raised CO2 levels in brain which may casue further aggravation of CNS stimulation leading to status epilepticus (7-10).

Thus, ES poisoning should be suspected in the presence of primary central nervous system manifestations including seizures. It is very important to follow basic principles of treatment of poisoning with CNS stimulants ie. to look and timely treatment of hypoglycemia, hypoxia, cerebral edema & Metabolic abnormalities to prevent permanent neurological damage in such patients.

Fig 1 & 2 shows Marked Cortical Atrophy & Volume Loss in one of our patients on MRI. The CNS stimulation produced by ES intoxication is by inhibiting Ca- and Mg-ATPase and antagonising chloride ion transport in gamma-aminobutyric acid (GABA) receptors with little or no peripheral component. The neurotoxicity of ES has been attributed alterations in the serotoninergic system and inhibition of sodium, potassium dependent ATPase enzymes in brain also (7). Blanco-Coronado *et al* (11) reported hyperglycemia in six cases with ES intoxication and also reported high anion-gap metabolic acidosis in six patients with ES intoxication. Ugur Koca *et al* (7) among their two cases of ES, experienced hyperglycemia in second case and hypocalcemia in both cases & metabolic acidosis. Their first case because of treatment with sodium bicarbonate before admission to ICU did not result in metabolic acidosis. The results are in accordance with one of our case whose MRI is shown as far metabolic acidosis and hypocalcemia is concerned. However, in our case we reported hypoglycemia as

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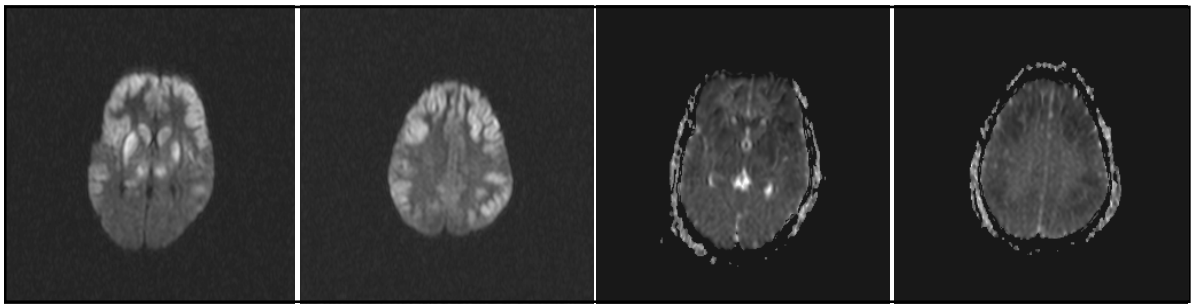

Fig 1. Diffusion Weighted Imaging (DWI) and Apparent Diffusion Coefficient (ADC) Maps Confirm Cytotoxic Edema of Cortical Grey Matter and Deep Grey Matter

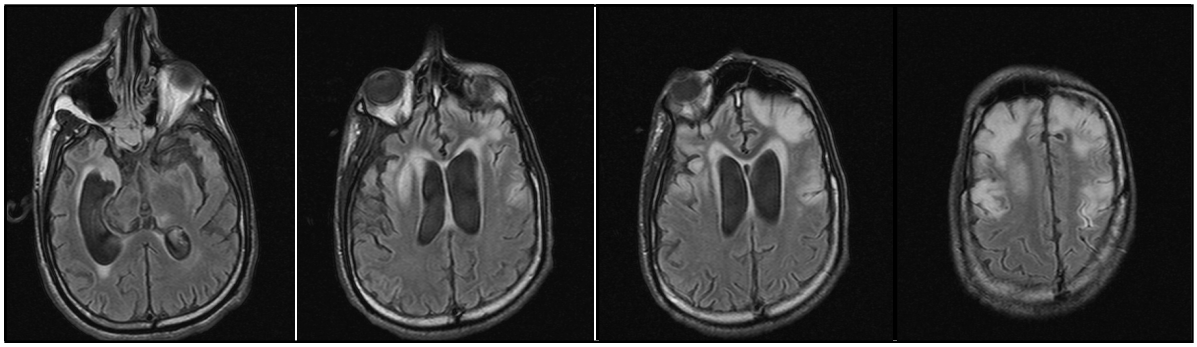

Fig 2. FLAIR Axial Images Show Marked Cortical Atrophy & Volume Loss With Increased Signal Intensity of Cortical & Deep Grey Matter

presenting features unlike above two cases. Severe metabolic acidosis supports the interference of the agent with the cellular metabolism and oxygen consumption. Thus anoxia leading to metabolic acidosis and acidosis leading to anoxia may be the contributing reason for status epilepticus. The rapid correction of metabolic acidosis may prevent neurological damage.

Haun *et al* (12) reported diffuse cerebral edema and hypoxia in a fatal toxaphene, poisoning, which may also be responsible for status epilepticus. At cellular level, organochlorines may inhibit enzyme activities of the mitochondria by stimulating the production of ROS, and this mechanism has been implicated in the immunotoxicity, hepatotoxicity and carcinogenecity of these chemicals (3-10). Serum liver function tests elevated in cases of Ugur Koca *et al* (7). Though there is no specific antidote for this poison but NAC works in this poison almost as an anti- dote. Thus, NAC treatment should be started immediately(150 mg kg $^{-1}$ body weight with 15 min, 50 mg kg -^{1} weight with 4 hours, 100 mg kg $^{-1}$ body weight with 16 hours). NAC, serves as a precursor for glutathione and, thus, can replenish the intracellular glutathione stores and thus can act as a direct scavenging agent and can produce antioxidant and cytoprotective effects. Furthermore, NAC may stimulate endothelium-derived relaxing factor and improve microvascular blood flow, increases hepatosplanchnic blood flow, decreases peroxidative stress, attenuates the increase in S-transferase and circulating ICAM-1 and VCAM-1 after reperfusion of the liver (7).NAC also attenuate the increase in the brain levels of malondialdehyde (MDA) and the increase in the hippocampus of myeloperoxidase (MPO) caused by cerebral ischaemia (13, 14).

Benzodiazepines and barbiturates can be used for controlling the initial seizures in ES intoxication. Boereboom *et al* (14) reported use of thiopentone (i.v. 10 mg kg -1 body weight bolus over 6 minutes followed by i.v. 20 mg kg -1 body weight over 30 minutes with i.v. maintenence therapy of 5-10 g day -1) in ES intoxication. Phenytoin is probably less effective in these cases, given the effect of ES on GABA receptors (15). Sood *et al* (15) reported a case of ES poisoning presenting with status epilepticus. Their case had a complete recovery with symptomatic treatment. Where as, in study of Ugur Koca *et al* (7), seizures were controlled with benzodiazepine, and none of the patients developed status epilepticus. Midazolam, pheytoin remain main treatment as antiepileptic (16).

Role of PAM is controversial in organochlorine poisoning: Administering pralidoxime and atropine to patients poisoned with organochlorines and pyrethroids may be harmful, is unlikely to provide any beneficial effect, and wastes resources (17).Thus, in case of doubt antibodies to acetyl choline receptor can be studied and if found on higher side then only PAM should be administered.

Neuroprotective agents: The epileptogenesis is a dynamic process, & offers a useful window for application of promising neuroprotective strategies. Ideally, the initial insult modification strategy should be efficacious for inducing anti-seizure, antiepileptogenic and disease-modifying effects. Among the new generation AEDs, only topiramate (TPM), lamotrigine (LTG) and vigabatrin (VGB) seem to have some anti-epileptogenic along with neuroprotective effects (18). All these remain experimentally to be proved as neuroprotective. No well established drugs against neurodegenerative changes and/ or neuro-protective drugs against hypoxia and metabolic degenerative injuries of brain as a result of such posion.

There are very few isolated case reports and case series of accidental and suicidal poisoning with Endosulfan (ES) in the literature. The predominant toxicological effect is over-stimulation of the central nervous system (CNS). There exist dilemmas among emergency clinicians and intensive care units, difference of opinion & lack of consensus in treatment guidelines, of this relatively uncommon poisoning which often lead to permanent lifelong morbidity or even mortality. There is an urgent need to develop treatment protocol consensus/ guidelines of most common as well as uncommon poisons like ES in the interest of Mankind.

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