Antioxidant Treatment With N-Acetylcysteine In Endosulfan Intoxication: Report Of Two Cases

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Citation

Abstract

Objective: Organochlorine compounds may cause oxidative stress by stimulating the production of reactive oxygen species. This mechanism has been implicated in the immunotoxicity, hepatotoxicity and carciogenecity of these compounds. Endosulfan is an organochlorine insecticide with potential toxicity for central nervous, cardiopulmonary system and liver and kidney. Endosulfan induces T-Cell apoptosis, mitochondrial dysfunction, oxidatif stress and lipid peroxidation. N-acetylcysteine (NAC) is an antioxidant agent replenishes the intracellular gluthathione stores. Thus, we reported the potential benefits of antioxidant treatment with NAC in endosulfan intoxication.

Setting: Multidisciplinary intensive care unit of the University Hospital
Patients: 16- and 17- year old comatose patients with generalized tonic-clonic convulsions, metabolic acidosis, hyperlactatemia, hypocalcemia, elevated liver and muscle enzymes, trombocytopenia, leukocytosis, normal serum pseudocholinesterase activity, tachycardia and hyperthermia.
Interventions: NAC (150 mg kg-1 body weight with 15 min, 50 mg kg-1 body weight with 4 hours, 100 mg kg-1 body weight with 16 hours) intravenously and cholestyramine 16 g day-1 perorally treatment with standard intensive care unit care.

Results: One of the patients survived, the other patient who ingested highest amount of endosulfan in the literature died. Treatment with N-acetylcysteine improved organ functions and reduced logistic organ dysfunction scores in two cases.

Conclusion: We observed rapid reduction in organ dysfunction parameters and logistic organ dysfunction scores in our two cases suggesting that the potential benefits of NAC as an antioxidant agent in endosulfan intoxication.

INTRODUCTION

Organochlorine compounds are fat-soluble chemical compounds and seperated in six groups; dichlorodiphenyltrichloroethene, hexachlorocyclohexane, chlordecone, toxaphene, dicofol and cyclodienes. They are stored in the adipose tissue and resistant to degradation [1,2].

Endosulfan ($C_9H_6Cl_6O_3S$) is a highly toxic organochlorine belonges to cyclodienes group and devoleped in 1954 under the name of Thiodan [1]. It has been shown that endosulfan induces T-cell apoptosis, mitochondrial dysfunction and oxidative stress [3,4] and lipid peroxidation [5,6].

The cases with acute endosulfan intoxication, accidentally or suicidally, have been reported in literature. The use of the therapeutic modalities such as gastric lavage, activated charcoal, mechanical respiratory assistance, and the agents such as benzodiazepines and barbiturates for seizures have also been reported in endosulfan intoxications [1,7,8,9].

N-acetylcysteine (NAC) is a thiol, which is a precursor of L-cysteine and reduced glutathione. NAC is a source of sulphydryl groups in cells and scaveneger of free radicals as it interacts with reactive oxygen species (ROS) such as hydrogen peroxide and hydroxyl radical [10]. It has been shown that administistration of NAC prevents liver damage and significantly reduces mortality in acetaminophen overdose [11].

Besides the traditional agents and therapeutic modalities we additionally used NAC in two cases of endosulfan intoxication, because of the therotical benefits of NAC to protect the liver from oxidative injuries.

In our extensive literature search we could find any data

about the use of NAC in the treatment of endosulfan intoxication. We aimed to report two cases with endosulfan intoxication to discuss the potential benefits of NAC as an antioxidant agent and to review the literature of endosulfan intoxication.

CASE REPORT
CASE 1

A previously healthy 16-year-old man was admitted to a hospital for suicidal ingestion of approximately 100 ml (514 mg kg-1 body weight) of Hektionex 36 EC (endosulfan 360 g L^{-1}) at 07:00 AM. His vital and laboratory findings obtained from history were as follows; On admission at 08:00 AM, the patient was unconsciosness and had generalized tonic-clonic convulsions. Glasgow coma scale was 3 out of 15, pupils were fix-dilated and nonreactive to light, blood pressure (BP) was 120/70 mm Hg, hearth rate (HR) was 170 bpm. Laboratory tests were arterial pH: 6.95, P_aCO_2: 8.38 kPa, serum bicarbonate: 14 mmol L^{-1}, blood leukocyte cell count: 31 $10^9 L^{-1}$, blood hemoglobine: 13.8 g dl^{-1}, blood platelet count 16.8 $10^9 L^{-1}$, blood glucose: 3.94 mmol L^{-1}, blood urea nitrogen: 6.39 mmol L^{-1}, serum creatinine: 141.4 µmol L^{-1}, serum alanine aminotransferase: 26.17 µkat L^{-1}, serum aspartate aminotransferase: 25.12 µkat L^{-1}, serum creatine kinase (CK): 68.4 µkat L^{-1}, CK-MB: 6.65 µkat L^{-1}, serum sodium: 148 mmol L^{-1}, serum potassium: 4.5 mmol L^{-1}. He has been treated with 270 mEq $NaHCO_3$, 10 mg h^{-1} IV artopine infusion, 1 g pralidoxime and gastric lavage with activated charcoal performed for suspected anticholinesterase poisoning. Serum cholinesterase activity was normal at 122.38 µkat L^{-1} (normal range: 73.35-225 µkat L^{-1}). After the blood sampling for labarotory investigations, cardiopulmonary resuscitation (CPR), was performed 12 times with 5-10 minutes because of cardiac arrests. Blood gases analysis after CPR were pH: 7.17, P_aCO_2: 4.12 kPa, P_aO_2: 9.31 kPa, HCO_3: 11 mmol L^{-1}. He was transported to our university hospital for mechanical ventilatory asisstance.

On admission at 11:00 PM to our university hospital emergency service, his Glasgow coma scale 3 out of 15, blood pressure 87/34 mm Hg, hearth rate 116 bpm, pupils were fix-dilated and nonresponsive to light. On mechanical ventilation (pressure regulated volum control, fiO_2: 0,7) blood gas analysis were pH: 7.48, P_aCO_2: 2.58 kPa, P_aO_2: 34.71 kPa, HCO_3: 14.7 mmol L^{-1}. A cranial computed tomography scan revealed diffuse cerebral edema. At 12:00 PM hia blood pressure was 44/27 mm Hg and epinephrine 0.1 mg was given and dopamine 5 g.kg $^{-1}$ .min $^{-1}$ and dobutamine 5 g kg $^{-1}$ min $^{-1}$ was started. His serum cholinesterase activity was normal at 122.7 µkat L^{-1}. At 00:30 AM he was transported to intensive care unit (ICU), with his blood pressure 140/70 mm Hg, hearth rate 109 bpm.

On admission to ICU, glasgow coma scale was 3 out of 15, pupils were fix-dilated and unresponsive to light, body temperature was 36 C. Laboratory and clinical findings of the case 1 during the ICU treatment were outlined in table 1. Mechanical ventilation, gastric activated charcoal and antiedema (20% mannitol) treatment was started. At the 12 th hour of admission to ICU, urine output was approximately 500 ml h $^{-1}$, urine specific gravity (SG): 1005 and serum sodium: 150 mmol L^{-1}. We started desmopressin treatment and fluid ressusication for diabetes insipidus. At the14 th hour of admission to ICU, we started NAC treatment (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) ($_{12}$) and cholestyramine 16 g day $^{-1}$ perorally. We started dopamine infusion (15 g kg $^{-1}$ min $^{-1}$) at fourth day of admission to ICU and epinephrine (0.03-0.05 g kg $^{-1}$ min $^{-1}$) at seventh day of admission to ICU for refractory hypotension despite of optimal fluid resussication. At 150 th hour of admission to ICU brain death tests were started, but he died at the 155 th hour.

Figure 1

Table 1: Laboratory and clinical findings of first case

	Normal range	1.day	2.day	3.day	4.day	5.day	6.day	7.day
LOD score		16	11	11	9	9	9	11
Blood urea nitrogen (mmol L⁻¹)	2.14-7.14	11.78	10.71	10.42	9.99	11.42	11.98	12.49
Serum creatinine (µmol L⁻¹)	70.7-123.7	188.3	163.5	159.1	125.5	139.6	106	102.2
Blood glucose (mmol L⁻¹)	3.88-6.1	5.44	8.21	6.32	5.6	6.55	6.98	6.16
Serum sodium (mmol L⁻¹)	136-148	144	150	139	141	161	154	140
Serum potassium (mmol L⁻¹)	3.5-5.5	4.09	4.7	4.6	3.33	4.28	3.5	3.45
Serum ionized calcium (mmol L⁻¹)	1.13-1.32	0.49	0.85	0.84	0.78	0.93	0.91	
Serum chloride (mmol L⁻¹)	96-110	110	109	109	111	126	121	111
White blood cell count (10⁹ L⁻¹)	4-10.3	23.7	12.7	10.4	10.4	8.4	8.1	24.1
Platelet count (10⁹ L⁻¹)	156-373	90	66	65	67	92	96	89
Prothrombin time (sec)	10.5-13.5	30.7	25.5	16.2			15.7	
APTT (sec)	25-35	50.8	35.7	38.2		41.1		
International normalized ratio	0.83-1.13	2.663	2.175	1.327		1.28		
Plasma fibrinogen (g L⁻¹)	2-4		3	6.24		6.35		
Serum albumin (g L⁻¹)	39-51	35	32	31	32	32	31	
Serum cholinesterase (µkat L⁻¹)	73.35-225	122						
Serum total bilirubin (µmol L⁻¹)	1.71-20.52	4.4	11.2	9.9	13.34		12.48	21.2
AST (µkat L⁻¹)	<0.633	38.99	46.54	6.15	4.58	1.66	1.28	0.85
ALT (µkat L⁻¹)	<0.68	28.1	15.7	11.25	9.23	4.86	4.15	3
ALP (µkat L⁻¹)	0.56-4.5	7.26	6.3	6.28		6.1	5.9	
LDH (µkat L⁻¹)	4-8	65.67	29.6	24.9		29.5	29.7	
GGT (µkat L⁻¹)	0.19-0.81	0.41	0.41					
CK (µkat L⁻¹)	0.43-3.16	288.8	201.3	108.3		9.6	8.26	
CK-MB (µkat L⁻¹)	0-0.41	>8.33	6.45	5.25				
Serum troponin T (ng ml⁻¹)	0.03-0.1	55.7	12.4	8.7				
Serum myoglobin (ng ml⁻¹)	25-72	>800	>800	>800				
Arterial lactate (mmol L⁻¹)	0.5-1.2	3.7	1.1		0.4			
Body temperature (axillary-C°)		36.8	37.2	36.3	37.3	38	36.4	38
Systolic blood pressure (mm Hg)		130	90	100	90	130	80	70
Heart rate (bpm)		200	200	120	140	130	160	190

APTT= activated partial thromboplastin time, AST= serum aspartate aminotransferase, ALT= serum alanine aminotransferase, ALP= serum alkaline phosphatase, LDH= serum lactate dehydrogenase, GGT= serum gamma-glutamyl transpeptidase, CK= serum creatine kinase

CASE 2

A previously healthy 17-year-old man was drunk water which mixed with Megasulfan HC-36 (endosulfan 360 g L^{-1}) accidentally at 10:40 PM. On admission to our university

emergency service at 02:00 AM, his Glasgow coma scale was 3 out of 15, pupils were fix-dilated and responsive to light, he had generalized tonic-clonic convulsions. Endotracheal intubation and cardiac defibrilation by 200 J were performed for ventricular fibrillation. CPR was performed with 3 minutes. Diazepam 10 mg and thiopenton 200 mg were given to control convulsions. On admission to ICU at 03:00 AM, his blood pressure were 185/115 mm Hg, hearth rate was 170 bpm, body temperature was 36 C , Glasgow coma scale 3 out of 15, pupils were fix-dilated and unresponsive to light and he had generalized tonic-clonic convulsions. Blood gases analysis were pH: 7.08, , P_aCO_2: 5.65 kPa, P_aO_2: 30.38 kPa, HCO_3: 12.8 mmol L^{-1} , oxygen saturation: 0.99 and anion gap were 32 mmol L^{-1} . And then we treated high anion gap metabolic acidosis with 200 mEq $NaHCO_3$. Laboratory and clinical findings of the case 2 during the ICU treatment were outlined in table 2. A computed tomography scan of the cerebrum was normal.We controlled convulsions by infusion of thiopenton infusion 75-200 mg h^{-1} with 54 hours. Mechanical ventilation, activated charcoal was started. At the14th hour of admission to ICU, we started NAC treatment (150 mg kg^{-1} body weight with 15 min, 50 mg kg^{-1} body weight with 4 hours, 100 mg kg^{-1} weight with 16 hours) and cholestyramine 16 g day^{-1} perorally. At the 7th hour of admission to ICU, we infused dopamine 15 g kg^{-1} min^{-1} with 9 hours for refractory hypotension to optimal fluid resuscitation. He regained consciousness within 80 hours of admission to ICU and was extubated after 7 hours. At 7 day after admission to ICU he was discharged to the medical ward.

Figure 2

Table 2: Laboratory and clinical findings of second case

	1.day	2.day	3.day	4.day	5.day	6.day	7.day
LOD score	9	9	1	1	1	1	1
Blood urea nitrogen (mmol L^{-1})	3.9	6.7	4.6	3.2	3.2	3.9	4.6
Serum creatinine (µmol L^{-1})	119.3	108.7	70.7	56.5	54.8	53.9	50.3
Serum sodium (mmol L^{-1})	145	155	147	146	136	139	143
Serum potassium (mmol L^{-1})	3	4.2	3.6	3.6	4.4	3.7	3.8
Serum ionized calcium (mmol L^{-1})	0.59	1	0.79	1	1	0.71	0.78
Serum chloride (mmol L^{-1})	104	122	108	110	102	102	102
Serum bicarbonate (mmol L^{-1})	12	22					
Anion gap (mmol L^{-1})	32	15.2					
Arterial lactate (mmol L^{-1})	13.6	1.7	0.9				
Blood glucose (mmol L^{-1})	16.7	6.77	5.27	6.16	7.77	7.9	6
White blood cell count (10^9 L^{-1})	21	10.9	6.5		6.1	6.9	7.6
Platelet count (10^9 L^{-1})	379	190	126		130	178	224
Serum albumin (g L^{-1})	45		28		35		35
Serum cholinesterase (µkat L^{-1})	20.13						
Prothrombin time (sec)	13.5		16.6				
APTT (sec)	42.7		39.2				
International normalized ratio	1.088		1.36				
Fibrinogen (g L^{-1})	2.21		7.25				
Serum total bilirubin (µmol L^{-1})	1.71		11.8		6.49	5.98	7.5
AST (µkat L^{-1})	1.25	2.55	2.71	1.6		1.1	
ALT (µkat L^{-1})	0.98	1.18	1.56	1.15	1.35	1.2	
ALP (µkat L^{-1})	5.75		3.53				
LDH (µkat L^{-1})	9.18		11.9				
GGT (µkat L^{-1})	1.23						
CK (µkat L^{-1})	5.36	74.4	52			9.33	
Systolic blood pressure (mm Hg)	190	160	120	120	130	140	140
Heart rate (bpm)	190	150	100	95	100	100	105
Body temperature (axillary- C°)	39	37.8	37.9	37.3	37	37.1	36.5

DISCUSSION

Accidental lethal intoxication with endosulfan was first described in humans in 1974 by Terziev et al ([13]). The reported signs in humans after endosulfan intoxication previously in literature include: abdominal pain, nause, womiting, foamy oral fluid, chest pain, sinus tachycardia, hypertension ([7,8]), miosis (which maybe followed by mydriasis), hyperglycemia, elevated activity of liver enzymes ([1,7,9]), hyperthermia ([1,7,14]), rhabdomyolisis ([9]), acute interstitial nephritis ([15]), acute tubular necrosis ([1,8]), metabolic acidosis combined with a elevated anion gap ([1,7]), hyperlactatemia ([7]), respiratory dystress, respiratory arrest, tremor, ataxia, convulsions, unconsciousness ([1,7,8,9]), normal level of serum pseudocholinesterase activity ([7]), leukocytosis ([7,8]) and trombocytopenia ([1]). In addition, we experienced elevated serum lactate dehydrogenase (LDH), CK and CK-MB activity and troponin –T and decreased serum ionized calcium level not reported in previous cases. At cellular level, organochlorines may inhibit enzyme activities of the mitochonrial electron transport chain ([16]). Imbealut et al ([17]) reported that increased plasma organochlorine levels were significantly corelated with reduced oxidative enzyme activities of skeletal muscle in man. Organochlorine related rhabdomyolisis has been reported previously in human ([9,18]). Elevated serum CK and LDH levels was probably related to the muscle injury in our cases. Severe rhabdomyolisis in our first case, as judged by highly elevated serum CK, LDH, and myoglobin may be releated to prolonged anoxia or toxicity

of extremely high amount of ingested endosulfan. Rapid decrease of muscle enzymes in our cases may be attributed to antioxidant effects of NAC treatment. Although elevated serum CK-MB activity and troponin-T levels in our first case may be attiributed to myocardial injury by CPR, we didn't experience any ischemic electrocardiographic changes in our cases.

Garg et al [19] demonstrated that the high dose of endosulfan (40 mg kg^{-1}) significantly decreases the plasma calcium level with 35% at 4 h after ingestion in rats. We also experienced decreases in plasma levels of ionized calcium in our cases.

Organochlorine compounds have the ability to cause oxidative stress by stimulating the production of ROS, and this mechanism has been implicated in the immunotoxicity, hepatotoxicity and carcinogenecity of these chemicals [20,21,22,23]. ROS are produced primaryl by the mitochondria in cells as a by-product of normal metabolism during conversion of molecular oxygen to water. These include: superoxide radical, hydrogen peroxide, hydroxyl radical. The mean antioxidative enzymes are catalase which converts hydrogen peroxide to molecular oxygen and water, glutathione peroxidase (GPx) which converts hydrogen peroxide to water, coupled to the oxidation of reduced glutathione to oxidized glutathione, and superoxide dismutase (SOD) which converts superoxide radical to hydrogen peroxide [24]. Endosulfan reduced erythrocyte, lung and liver SOD activity and lung and liver glutathione (GSH) levels in rat [4]. In adrenocortical cells of rainbow trout (Oncorhynchus mykiss), endosulfan reduced GPx activity and GSH level and increased the activity of glutathione transferase, also increased lipid hyperperoxides levels [5]. In rats, single dose of 30% LD$_{50}$ endosulfan increased thiobarbituric acid reactive substance (TBARS) in cerebral and hepatic tissues [6]. The other organochlorine insecticide chlordane increased serum skeletal muscle related creatinine phosphokinase and lactate dehydrogenase activities and lipid peroxidation in rat liver [25]. Sahoo et al [26] demonstrated that Hexachlorocyclohexane (HCH) is an organochlorine compound that induces oxidative stress in rat cerebral hemisphere, as judged by decreased cerebral catalase, SOD, GPx activity and GSH levels.

Serum liver function tests elevated in our two cases. Extremely high serum liver enzyme levels in first case may be due to ingestion of extremely high amount endosulfan with or without prolonged anoxia. Boerboom et al [7]

reported that congestion of liver with perivenular steatosis presumptively attributed to endosulfan intoxication at forensic outopsy. Elevations of serum transaminases in our second case identical to previously reported cases in literature [1,7]. Venkateswarlu et al [27] reported that the values of elevated serum transaminases returned to normal at the end of six weeks in forty four endosulfan poisoning. The organochlorine lindane causes an increase in activity of the pro-oxidant enzyme NADPH oxidase in isolated neutrophils [28] and in liver microsomal preperations [21,23]. In the liver this pro-oxidant activity is accompanied by lipid peroxidation and hepatocellular injury [21,23]. Similarly the other organochlorine dieldrin induces a state of oxidative stress in liver by causing an increase in the production of ROS with a concomitant decrease in antioxidant concentrations and an increase in hepatic DNA synthesis. Treatment with antioxidants attenuates all of these changes, suggesting the involvement of oxidant mechanisms in toxic and tumor-promoting effects of dieldrin [20,29]. Rapid decreases of elevated serum transaminases in our cases may be due to NAC treatment. NAC, serves as a precursor for glutathione and, thus, can replenish the intracellular glutathione stores [30]; however, NAC is also able to act as a direct scavenging agent [10]. Thus NAC produce antioxidant and cytoprotective effects, furthermore, NAC may stimulate endothelium-derived relaxing factor and improve microvascular blood flow [31]. In septic patients NAC increases hepatosplanchnic blood flow [32], decreases peroxidative stress [33], attenuates the increase in S-transferase and circulating ICAM-1 and VCAM-1 after reperfusion of the donor liver, indicating possible cytoprotective effects of NAC [34]. We used logistic organ dysfunction score (LOD), include neurologic, pulmonary, cardiovascular, renal, haemotologic and hepatic parameters, for assesing organ functions [35]. LOD scores decreased after NAC treatment in our both cases.

In rats [36] and cats [37] cerebrum had higher endosulfan concentration than cerebellum and remaining parts of brain. The neurotoxicity of endosulfan has been attributed to inhibition of the calmodulin-dependent Ca^{+2}-ATPase activity [38], alterations in the serotoninergic system [39] and inhibited GABA receptors [40]. Endosulfan is able to inhibit sodium-, potassium-, and magnesium-dependent ATPase enzymes in rainbow trout brain [41]. In cats, endosulfan produced high amplitude bursts of spike discharges in electrocorticogram. Changes in electrical activity on cerebral cortex attributed to the direct effect of the compound as the

concentration was highest in this area. The depletion of acetylcholine without any change in acetylcholinesterase activity might be due to the direct effect of endosulfan on the synthesis of acetylcholine [42]. Single oral administiration of endosulfan (15 mg kg $^{-1}$ body weight) to rats reduced phosphatidylinositol and phosphatidylinositol 4,5-bisphosphate without any significant effect on phosphatidylinositol 4-bisphosphate, suggest that possible phosphoinositide messsenger system in the neurotoxicity of endosulfan [43].

In humans convulsions begins 1-4 hours after endosulfan ingestion [1,7]. In our cases, tonic-clonic generalized convulsions began approximately 1 hour after endosulfan ingestion. Our first and second case admitted to intensive care unit 16 th and 3 th hour respectively after endosulfan ingestion with Glasgow coma scale of 3 out of 15 and their pupils were fix-dilated and nonreactive to light. We obtained diffuse cerebral edema in CT scan of first case that probably related to repeated cardiopulmonary resuscitation and toxic effect of organochlorine and brain CT scan of second case was normal. Also Haun et al [44] were obtained diffuse cerebral edema in a fatal toxaphene, another organochlorine, poisoning. In the first case, seizures have been obtained before admission to ICU, but we didn't experience seizures in ICU probably because of severe cerebral damage due to hipoxia and repeated cardiopulmonary resuscitation.

Benzodiazepines and barbiturates can be used for controlling the seizures in endosulfan intoxication. Pentobarbital was an effective therapeutic measure against an absolute lethal dose of endosulfan in rats, while diazepam was not effective [45]. Boereboom et al [7] reported use of thiopenton (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 endosulfan intoxication. In their case, the first day after admission the EEG showed persistent epileptic activity despite the anticonvulsive herapy. We infused 75-200 mg h $^{-1}$ thiopentone for 54 hours for controlled seizures in second case.

Our cases were treated with sodium bicarbonate because of metabolic acidosis. We experienced high anion gap metabolic acidosis in the second case and did not in the first case because of treatment with sodium bicarbonate before admission to ICU. Blanco-Coronado et all [1] reported high anion-gap matabolic acidosis in six patients with endosulfan intoxication. Our patients had severe metabolic acidosis supporting the interference of the agent with the cellular

metabolism and oxygen consumption [46]. The rapid correction of metabolic acidosis suggest however that anoxia due to the convulsions may be the primary cause of metabolic acidosis. Also we obtained hyperlactatemia in our cases that identical with previously reported case [7] that suggests altered cellular metabolism.

Endosulfan can be absorbed following ingestion, inhalation and skin contact. The LD_{50} of endosulfan varied widely depending on the route of administiration, species, vehicle and sex of the animal. The oral LD_{50} of endosulfan in rats ranges from 18-355 mg kg $^{-1}$ body weight [7,45]. Blanco-Coronado et al [1], reported that six patients with acute endosulfan intoxication. One of these patients whom blood endosulfan level was 2,85 mg L $^{-1}$ (mean= 0,48 mg L $^{-1}$) had died. Boereboom et al [7] reported a case that nonaccidental ingestion of endosulfan 260 mg kg $^{-1}$ body weight had died. Our first case ingested 514 mg kg $^{-1}$ body weight endosulfan and this is the highest amount of endosulfan ingestion in literature. Male rats given a single oral dose of endosulfan at 40 mg kg $^{-1}$ body weight displayed neurotoxic manifestations and showed a significant increase in blood glucose, blood ascorbic acid and blood and brain glutathione and decrease in plasma calcium levels [19]. Blanco-Coronado et al [1] reported hyperglycemia in six case with endosulfan intoxication. We also experienced hyperglycemia in second case and hypocalcemia in both case.

Following acute over-exposure high endosulfan concentrations can temporarily be found in the liver; the concentration in plasma decreases rapidly [45]. The tissue distribution of endosulfan in a case who died with 6 hours after ingestion was maximum in liver followed by kidney, urine and blood [47].

Therapeutic modalities such as carefully performed gastric lavage with tap water followed by salin purgatives, multipl doses of activated charcoal to minimize systemic absorbtion of the toxin, cholestyramine, nonabsorbable bile acid binding exchange resin for enhance fecal elimination of the toxin by interrupting the biliary-enterohepatic and enteroenteric recirculation, can be used for the treatment. We also used activated charcoal and cholestiramine in our cases.

In conclusion, the severity of organ injury related to endosulfan intoxication may be corelated with the amount of ingested agent. NAC, as an antioxidant agent may be a supplemental treatment strategy of endosulfan intoxication related organ dysfunction. This suggestion needs further controlled experimental investigations.

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