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CLINICAL STUDY

Unintentional endosulfan poisoning

Salim Satar[1], Ahmet Sebe[1], Nezihat Rana Alpay[1], Umut Gumusay[1], Ozlem Guneysel[2]

Cukurova University, School of Medicine, Department of Emergency Medicine, Balcali-Adana, Turkey.
guneysel@gmail.com

Abstract: Endosulfan is an organochloride insecticide, widely used in insect control. It is responsible for many severe intoxication and several deaths. We present a case series of endosulfan poisoning, admitted to our emergency department with different clinical courses. Two patients presented with status epilepticus and were successfully treated with thiopental sodium to control seizures. One patient required also hemodialysis. All patients were discharged following a complete recovery of their health. Endosulfan is a highly toxic insecticide that produces tonic-clonic convulsions, headache, dizziness and ataxia. It can cause also life threatening metabolic disturbances. Treatment is symptomatic and supportive *(Tab. 2, Ref. 11).* Full Text (Free, PDF) *www.bmj.sk.*
Key words: emergency, endosulfan, hemodialysis, poisoning, status epilepticus.

Organochloride insecticides are chlorinated cyclic hydrocarbons. These highly toxic compounds are responsible for many severe intoxication and several deaths worldwide. Endosulfan is an organochloride insecticide, widely used in insect control and is absorbed by both humans and animals through the intestinal tract, lungs, and the skin (1). Case series of endosulfan poisoning are rare in literature. In this study we present 6 patients from the same family with unintentional endosulfan poisoning after ingesting the soup with endosulfan. Two patients presented with status epilepticus and metabolic acidosis; one patient needed an urgent haemodialysis.

Cases

We present a case series of endosulfan poisoning consisting of 7 patients, one of them was dead on the arrival to the emergency department. The remaining 6 patients were previously healthy females, presented with abdominal pain, nausea, vomiting and paresthesia following last meal, the soup, which was prepared with flavor contaminated with endosulfan, a pesticide. Two patients, described as patient 1 and 2 in the Table 1, were admitted with generalized seizure and coma, and their cardiac, respiratory and circulatory functions were abnormal. Both of them had tachycardia, hypertension, tachypnoe and fever. The remaining four patients, who were alert, did not experience seizures. The first two patients had elevated creatine phospho kinase (CPK) and amylase levels on arrival. Due to the similarity of symptoms; elevated exocrine secretions and seizures, serum pseudocholinesterase levels were detected and were normal in all patients (Tab. 1). Biochemical and hematological analyses of the patients, with initial and final results are shown in the Table 1. Blood gases analyses of the patients (Tab. 2) revealed different results, such as decompensated metabolic acidosis in the patient 1, with different levels of compensation in other patients. Seizures in the patient 1 persisted despite the therapy with benzodiazepines and phenytoin. General anesthesia with sodium thiopental was used to control seizures and was successful. Medical therapy with bicarbonate was initiated to control metabolic acidosis in the same patient. However, medical interventions were insufficient to control acidosis and hemodialysis was performed once. Phenytoin was used to control seizures in the patient 2, since benzodiazepines were ineffective. CPK enzyme levels were elevated on arrival and during hospitalization in the patients 1 and 2 due to ongoing seizures. Patients were closely monitored for renal functions and hydrated with crystalloid fluids. All were hospitalized, patient 1 for 5 days; patient 2 for 4 days and other four patients for 2 days. No complications occurred and all patients were discharged with previous health status.

Discussion

Organochlorine pesticides antagonize the major inhibitory neurotransmitters, gamma amino butyric acid (GABA) and glycine.1 Binding of these pesticides to glycine and GABA-A gated chloride channel reduces influx of chloride ions, leading to neuronal hyperexcitability and toxicity (1). Clinical effects of organochlorine poisoning are predominantly seen as gastrointestinal and neurological toxicity; convulsion is a common and severe manifestation. Endosulfan is a polychlorinated hydrocarbon pesticide used in agriculture. Clinical effects from exposures to en-

[1]Cukurova University, School of Medicine, Department of Emergency Medicine, 01330, Balcali-Adana, Turkey, and [2]Marmara University, School of Medicine, Department of Emergency Medicine, Istanbul, Turkey

Address for correspondence: Ozlem Guneysel, Marmara Universitesi Hastanesi, Tophanelioglu C Yurtacan S No 13-15, Altunizade, Uskudar, Istanbul, Turkey.
Phone: +90.216.3271010, Fax: +90.216.3269578

Tab. 1. The biochemical, hematological and coagulation tests of the patients.

Parametrs	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6	
(normal values)	initial	final	initial	final	initial	final	initial	final	initial	final	initial	final
Glc (70–105 mg/dL)	293	100	108	87	114	95	142	132	157	134	122	105
tBil (<1 mg/dL)	0.2	0.35	0.3	0.2	4	0.3	0.3	0.3	0.2	0.6	0.5	0.5
dBil (0–0.2 mg/dL)	0.1	0.02	0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
AST (0–40 U/L)	19	31	18	20	22	18	29	28	15	15	29	25
ALT (<40 U/L)	9	30	19	9	11	10	18	18	8	10	42	35
LDH (160–500 U/L)	811	165	674	273	426	285	421	387	315	341	379	377
Amylase (28–100 U/L)	228	105	168	110	110	68	39	39	71	77	69	59
BUN (8–25 mg/dL)	13	12	17	9	9	7	5	4	11	25	14	11
Cr (0.8–1.2 mg/dL)	1.2	0.5	1	0.5	0.7	0.5	0.5	0.6	0.5	1.1	0.6	0.6
Na (135–145 mmol/L)	142	137	143	139	136	138	139	138	137	140	138	138
K (3.5–5.1 mmol/L)	4	4.2	3.1	3.6	4	3.4	4.1	3.8	3.8	4.4	4.1	3.9
CPK (<170 ng/mL)	10043	1021	1505	882	280	202	115	344	138	114	110	92
tCa (8.8–10.2 mg/dL)	7.95	9.1	7.87	7.69	8.47	8.35	7.69	9.04	7.72	9.7	9.77	9.11
iCa (1.1–1.3 mmol/L))	1.13	1.23	1.44	1.13	1.08	1	1.1	1.17	1.13	1.21	1.24	1.15
PCHE (6400–15500 U/L)	5395	6674	5095	6500	8384	8044	7932	7347	8409	8627	9654	10693
PT (11–15 sn)	22.5	12.7	18.7	21.2	16.8	14.6	34.2	12.9	18.7	15.2	12.4	13.6
INR (<2)	1.849	1.008	1.52	1.736	1.357	1.16	2.882	1.025	1.52	1.22	0.983	1.152
APTT (22.6–35 sn)	31.3	33.8	25.1	28.1	24.6	26.8	238	34.2	26.6	24.3	46	34
WBC (4.3–10.3 uL)	18700	12100	10400	9000	12700	9100	7000	10100	12000	5800	8300	6200
Hgb (14.5 g/dL)	12.2	11.8	12.7	13.5	14.2	13.6	12.1	13.8	12.3	12.1	12.8	12.7
Hct (39.53–50.33 %)	37.3	35.1	38.6	39.3	41.7	39.9	37.9	39.6	36.9	37.6	37.6	37.8
Plt (156–373.3 uL)	255000	186000	178000	220000	284000	264000	319000	351000	185000	306000	294000	254000

Abbreviations: ALT – alanine transaminase; aPTT – activated partial thromboplastin time; AST – aspartate transaminase; BUN – blood urea nitrogen; CPK – creatine phospho kinase; Cr – creatinine; dBil – direct bilirubine; Glc – glucose; Hct – Haematocrit; Hgb – Haemoglobine; iCa – ionized calcium; Initial – Values on admission; Final – values before discharge; INR – international normalization ratio; K – potassium; LDH – lactic dehydrogenase; Na – sodium; PCHE – serum pseudocholinesterase; Plt – platelet; PT – prothrombine time; tBil – total bilirubine; tCa – total calcium; WBC – white blood cell count

dosulfan are usually noted within 6 hours. This rapid onset of action is attributed to endosulfan's rapid absorption and distribution to lipophilic depots, including the central nervous system (CNS). While the plasma half-life is only a few hours, its slow redistribution back to the circulation over many days prolongs the elimination, half-life and duration of toxicity (2). Endosulfan is both a substrate and inhibitor of the cellular efflux transporter P-glycoprotein (P-gp) (2). Increased xenobiotic levels are demonstrated in the brain of animals lacking Pgp, suggesting an important role of this transporter in regulating xenobiotics crossing the blood-brain barrier (2). This may allow endosulfan to enter and persist in the extravascular compartment of the central nervous system, with ongoing toxicity, despite low plasma levels. An acute toxicity of endosulfan may result in permanent neurological impairment (3). Predominant toxicological effect is over-stimulation of the CNS, by inhibition of the calcium- and magnesium-ATPase, and antagonism of chloride ion transport in GABA receptors with little or no peripheral component (4). Characteristic clinical signs following an acute exposure are indicative of CNS disturbances or over-stimulation. These signs include seizures, nausea, vomiting, abdominal discomfort, hyperesthesia of the mouth and face, tongue and extremities, headache, agitation, hyperactivity, impairment of coordination, confusion, dizziness, and myoclonus (4). Convulsions are common and severe manifestations (5). Two patients presented with status epilepticus. The optimum management of status epilepticus requires an early identification and treatment. Empirically, an intravenous administration of benzodiazepine, followed by phenytoin and/or Phenobarbital is the first-line treatment of status epilepticus (6). Other agents may be considered if seizures continue, for example propofol, paraldehyde, lidocaine, valproate, ketamine, and inhalational anesthesia. Efficacy studies and experience with these second line agents is limited. In resource-poor areas, antiepileptic drugs should be selected on the basis of their complications and ability to manage these agents safely. One of these two patients did not require anesthesia, seizures continued after administration of benzodiazepine and phenytoin. The other patient's seizures persisted and were controlled only after a general anesthesia. One of the members of the family was dead on arrival. A possible reason of death in this patient seemed to be a prolonged seizure and hypoxic events following aspiration of the gastrointestinal content, because the mouth of this patient was full of food particles and secretions.

Life-threatening cerebral edema may occur after the endosulfan poisoning. Hemodynamic instability seems to be related to peripheral circulatory collapse and cardiac dysrhythmia, probably caused by endosulfan-induced myocardial toxicity (7). Rapid initiation of the anticonvulsant therapy and adequate dosing may actually be more important for improving the outcome than the drugs selected (8). Prompt and adequate therapy may prevent progression to status epilepticus or curtail an established status epilepticus (8). No treatment has been shown to improve the outcome of status epilepticus, although there are few trials to draw clear conclusions (8). Seizure duration greater than one

Tab. 2. Arterial blood gases of the patients.

Patient	1	2	3	4	5	6
pH	7.08	7.24	7.38	7.35	7.38	7.41
pCO_2 (mmHg)	23	39	38	27	32	37
pO_2 (mmHg)	93	170	98	48	127	112
BE (mmol/L)	-21.4	-4.4	-4.6	-5.3	-5.6	-4.6
HCO_3 (mmol/L)	4.8	21	24	22	22.3	22.9
SO_2 (%)	90	100	98	100	100	100

hour is associated with an extremely poor outcome (8). It has been recommended that general anesthesia should be induced where persistent status epilepticus continues beyond 60–90 minutes despite an adequate administration of anticonvulsants (8). Metabolic acidosis has been reported due to endosulfan toxicity (9), but this is the second reported case of severe metabolic acidosis prompting the use of hemodialysis following the endosulfan toxicity. Metabolic acidosis is a frequently encountered urgent hemodialysis indication. The studies appear to have ensconced 7.10 as the definition of "severe" metabolic acidosis (10). Bicarbonate hemodialysis is preferred for severe metabolic acidosis. If necessary, sodium bicarbonate may be given during hemodialysis. The first case reported in literature had undergone urgent hemodialysis due to endosulfan toxicity and subsequent severe metabolic acidosis. The pH of the case was 6.95 and due to metabolic acidosis, this patient had respiratory problems which were resolved after haemodialysis. We chose bicarbonate hemodialysis in our case because of early, severe acidosis (pH 7.08) refractory to bicarbonate therapy, with no obvious underlying cause, suggesting a toxic compound exposure that might be treated with hemodialysis.

Headache, nausea, vomiting and abdominal pain had been observed in all 6 of our patients and these symptoms continued for eight hours and recovered spontaneously in four of them. In patients 1 and 2, these symptoms resolved after 24 hours. Endosulfan is toxic also to the liver, kidney and lung, and can cause rhabdomyolysis in higher doses (11). Liver function tests consisting AST or ALT could be abnormal (11). In our patients, there were not increased levels of AST and ALT. The severity of the symptoms reported in literature differs (6). It might be due to ingested dose of endosulfan (11).

In conclusion, endosulfan is a highly toxic organochlorine insecticide that produces well-known life threatening neurological symptoms of tonic-clonic convulsions, headache, dizziness and ataxia but can also cause gastrointestinal symptoms and life threatening metabolic disturbances. Treatment is symptomatic and supportive.

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