Fatal diquat intoxication

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Abstract

Background. Since the introduction of diquat in agriculture practice in 1960’s, about 40 cases of poisoning have been described in detail in medical literature. Case report. We presented two cases. A case one, a 35-year-old, previously healthy, woman ingested 14% diquat solution. The poisoning had fulminant course, consisted of severe stomachache, vomiting, cardiocirculatory shock, respiratory failure and cardiac arrest 20 hours post-ingestion. Autopsy revealed myocardial infarction, bronchopneumonia and incipient renal damage. A case two, a 64-year-old man developed severe gastroenteritis, corrosive lesions of mucosal surfaces, acute renal injury, arrhythmias, brain stem infarction and bronchopneumonia. The diagnosis of diquat poisoning was made retrospectively upon the clinical picture and identification of pesticides he had been exposed to. The patient died 18 days post-exposure. The most prominent findings on autopsy were pontine hemorrhage and infarction, bronchopneumonia, left ventricle papillary muscle infarction and renal tubular damage. Conclusion. Cardiocirculatory disturbances led to fatal complications, the heart and brain infarction. We pointed out the heart as one of the most severely affected organs in diquat poisoning.

Key words: diquat; poisoning; brain infarction; myocardial infarction.

Introduction

Diquat (1,1’-ethylene-2,2’-bipyridilium) is a nonselective bipyridyl herbicide. It acts as a potent redox cycler, generating superoxide anion and other redox products, which induce lipid peroxidation in cell membranes leading to cell death. Ingestion of bipyridil herbicides, diquat and paraquat may cause severe and fatal poisoning. These herbicides produce corrosive lesions as a local effect, but their systemic effects are much more dangerous. Paraquat is used more widely, and its multiorgan toxicity is well recognized. Diquat is not so commonly used, and less than 40 cases of poisoning are reported in detail in medical literature. Acute lethal doses (LD₅₀) for both compounds are of the same order of magnitude, but diquat does not produce progressive pulmonary fibrosis as paraquat, so it is considered less toxic ¹. Clinical manifestations of diquat poisoning include primarily gastroenteritis and acute renal failure, but in severe cases respiratory failure, cardiovascular collapse, dysrhythmias, seizures and coma with brain haemorrhage and infarction may develop.² ³

We reported two cases of fatal diquat intoxication, both with severe complications including myocardial infarction.
Case report

Case 1, a 35-year-old woman, was brought to the Emergency Department (ED) by ambulance. The patient was able to provide a history and it was positive only for depressive disorder. In a suicide attempt she ingested approximately 30 ml of a pesticide. Shortly after the ingestion, she developed a severe stomachache and felt extremely nauseated, vomited once. Gastric lavage was performed at the local medical centre, two hours post-ingestion. Her relatives brought along a bottle of ingested herbicide Reglone®, containing 14% water solution of diquat.

On presentation to ED about 7 hours after the ingestion, the patient was alert, restless, diaphoretic, pale, and in obvious abdominal distress. Oropharyngeal examination revealed erythema, without corrosive lesions. The lungs were clear to auscultation. Heart sounds were normal, heart rate was 120 beats/min and regular, blood pressure was 105/70 mmHg. The examination of abdomen revealed only moderate mid-epigastric tenderness. Bowel sounds were hyperactive. The rest of physical examination was unremarkable. The chest and abdominal radiography was normal. Electrocardiogram showed sinus tachycardia at 120 beats/min with minimal ST segment depression. The initial blood analysis revealed white blood cell count (WBC) 14.0 × 10³/mm³, red blood cell count (RBC) 4.3 × 10⁶/mm³, hemoglobin 11.3 g/dL, hematocrit 38.6%, and platelets 317 × 10³/mm³. Blood urea nitrogen (BUN) was 6.6 mmol/L, creatinine 547 μmol/L, sodium 139 mEq/L, potassium 5.4 mEq/L, glucose 11.5 mmol/L, AST 147 U/L, ALT 89 U/L. Values of cholinesterase decreased: AChE and plasma pseudocholinesterase (ChE) revealed measuring the activity of erythrocyte acetylcholinesterase (AChE) and plasma pseudocholinesterase (ChE) revealed normal values of 5 560 U/L, and 9 370 U/L, respectively. AST was 16 U/L, ALT 13 U/L and CK 94 U/L. Arterial blood gases analysis showed pH 7.226, pCO₂ 23.3 mmHg, pO₂ 130.5 mmHg, sO₂ 97.9%, ABE – 16.8, SB 10.1 mEq/L.

The patient was admitted to intensive care unit. Peripheral intravenous line was instituted and initially she was given 2 000 ml of normal saline and 250 mL of 8.4% sodium bicarbonate. The patient had been on a cardiac monitoring since admission. Sinus tachycardia at 130–150 beats/minute with diffuse ST segment depression was present. She was restless with severe stomach pain, so tramadol and diazepam were given. Despite the fluids replacement, the urine output was noted to be only 20 mL. On the 2nd day after exposure the patient became febrile, the temperature was 38.2º C and clinical and chest radiographic findings of bronchopneumonia developed. A small zone of dyssepsisalisation of tongue mucosa appeared. Similar erosion was noted sublingually, also. Despite fluid replacement and normal values of arterial blood pressure and central venous pressure, the patient remained oliguric with diuresis of 400 mL during the first day, and 100 mL during the second day of hospitalization.

Severe gastroenteritis, corrosive lesions of mucosal surfaces, the development of acute renal injury and bronchopneumonia observed in our patient, strongly suggested a possibility of poisoning by bipyridylium herbicides. By this
time, we contacted the patient's family and asked them to bring the pesticides he had used. The members of his family indicated a possibility of deliberate ingestion and brought along two marked bottles of pesticides containing organophosphorous compounds malathion and dimethoate, and an unmarked bottle containing a dark liquid. The patient recognized all of them as the pesticides he used. Toxicological analysis of the unmarked bottle content revealed a 26% solution of diquat dibromide. Blood and urine samples were taken at the same time, but no traces of diquat or organophosphorous compounds were proven.

Hemodialysis treatment was started on the 3rd hospital day because of a progressive renal failure. The patient became increasingly somnolent after the first hemodialysis. On the 4th day, during the second hemodialysis, supraventricular tachycardia of 150 beats/min with signs of myocardial ischemia (depression of ST segment and inverted T waves in leads D1, aVL and V2–V5 by ECG) occurred. The patient experienced respiratory arrest, so he was placed on mechanical ventilation. The treatment with propaphenon and verapamil resulted in slowing down the heart rate, but the signs of myocardial ischemia persisted. Deterioration of consciousness was progressive leading to deep coma. Computed tomographic brain scan performed on the next day revealed extensive hypodense lesions of brain stem, suggesting infarction in the pons and mesencephalon on the left side with marked oedema around hypodense area. In deep coma, on mechanical ventilation, treated with antibiotics, fluid infusions, hemodialysis and other symptomatic and supportive therapy, the patient remained stable in the following period. A total of eight hemodialysis treatments were necessary for the period of 10 days, and after that renal function started to improve. The highest values of BUN (55.6 mmol/L) and creatinine (1.075 μmol/L) were noticed on the 8th day post-exposure. The other laboratory disturbances indicating multinorgan toxicity were transient increase of blood total bilirubin reaching maximum value of 179 μmol/L on the 4th post-exposure day, and constantly increased values of serum amylose activity with peak value of 712 U/L on the 2nd hospital day. The activities of amino transferases and creatine phosphokinase were increasing with peak values reaching on the 4th day post-exposure (AST 129 U/L, ALT 93 U/L, CK 3753 U/L). On the 14th hospital day cardiac arrest happened. Sinus rhythm was established, but on the 18th day post-exposure cardiac arrest happened again and was refractory to the treatment.

Postmortem examination revealed abnormalities in the pons and region of the left capsula interna, which were purpuric by cut surface of brain. Microscopic examination revealed areas of hemorrhage in association with multiple confluent areas of infarction. A small erosion of tongue, and a couple of similar erosions of laryngeal, upper tracheal, esophageal and gastric mucosa surfaces were noted. Edema, congestion and patchy areas of consolidation, containing purulent material, were observed in the lungs. Microscopic examination revealed thickening of alveolar walls. Cut surface of heart showed recent infarction of left ventricle papillary muscle. Perivascular myocardial fibrosis was observed by histology examination, also. Liver histology was normal. Incipient fatty infiltration of pancreas and reactive hyperemia of spleen were noted. Histological examination of kidneys revealed partial acute tubular necrosis. Fat loss of the suprarenal glands tissue was also observed.

**Discussion**

The case 1 represents an acute fulminant poisoning by diquat. It is reported that the ingestion of large amount of bipyridyl herbicides may cause death within a day or two, and clinical picture is essentially the same for diquat as for paraquat.

The case 2 despite the anamnesis of organophosphorous pesticides exposure and the slight decrease of cholinesterase activity, in view of characteristic clinical course was diagnosed with severe bipyridyl poisoning. The route of exposure to diquat was dubious. Inhalation usually causes mild signs and symptoms of poisoning, and fatal outcome is unlikely in such cases. Corrosive lesions of tongue, sublingual mucosa, esophagus, stomach, larynx and trachea indicated these tissues contact with the poison. The patient allowed possibility of accidental ingestion of small quantity during spraying. Similar way of exposure with corrosive lesions of upper gastrointestinal tract and systemic intoxication has been reported. Anyway, in view of severity of poisoning and the information of possible depressive disorder provided from patient's family, it was more likely the case of intentional ingestion.

Initial clinical manifestations of diquat intoxication include severe gastroenteritis, followed by acute renal failure, as was noticed in both our patients. In the case 2 renal failure developed despite the adequate fluids replacement and normal arterial and central venous pressure, so we believe it was the consequence of diquat nephrotoxicity, rather than hemodynamic disturbances. In the case 1 it could be partially caused by inadequate perfusion, and because of fulminant course, full clinical image of renal damage did not developed. Discrepancy between normal BUN and high creatinine levels in this case probably was the artifact due to interference of diquat in the laboratory assay for serum creatinine. Toxicology analysis for diquat in patient's serum was not available, but this finding may indicate its presence in blood.

Early development of bronchopneumonia was noticed in both presented cases, and contributed to respiratory failure. Impaired respiratory function has been reported in the most cases of severe diquat poisoning. It may be the manifestation of an acute lung injury, like in other kinds of severe illness and trauma. Consequently, thickening of alveolar walls, as revealed by histology in the case 2, may develop. Though pulmonary fibrosis after intratracheal administration of diquat is reported, and paraquat and diquat share similar mechanisms of toxicity, experimental studies showed that diquat is not accumulated in the lung and does not produce progressive pulmonary fibrosis like paraquat.

Toxic effects of bipyridyl herbicides also include damage of liver, pancreas, heart and muscle. Signs of hepatotox-
icity, such as jaundice, elevations in serum aminotransferases and liver centrilobular necrosis, as well as the development of pancreatitis, have been reported in paraquat poisonings. In the case 2, transient elevation of serum bilirubin and increased activity of amylase were noted, but histological examination of liver and pancreas did not reveal significant damage. Activities of transaminases were increased concomitantly with CK activity elevation, indicating muscle damage rather than liver necrosis.

We point out heart damage, noted in both presented patients. Besides gastrointestinal, cardiocirculatory disturbances including hypotension, tachycardia, and myocardial ischaemia were the leading signs of poisoning in the case 1. Cardiovascular hypotension unresponsive to fluids and vasodilator drugs is described in similar cases, but myocardial infarction, what we proved by postmortem examination, was not described in these reports. The patient was previously healthy young woman, so we believe that the development of myocardial infarction shortly after diquat ingestion was the consequence of its toxicity. In the case 2, four days post-exposure, the patient developed cardiac arrhythmias, which were transient, but electrocardiographic signs of ischemia persisted. Concomitant elevation of enzyme activity also indicated myocardial infarction, and finally it was confirmed by autopsy.

At the time the patient became hemodynamically unstable, progressive deterioration of consciousness was noted. Computerized tomography revealed infarctions in regions of pons and left capsula interna. There have been reports on pontine infarction or hemorrhage after diquat ingestion. In discussion, the brain stem damage was attributed to the possible effects of diquat itself or hemodynamic disturbances (hypo-perfusion and extracorporeal procedures). In our case myocardial ischemia and cardiocirculatory disturbances preceded significant central nervous system damage consistent with infarctions and hemorrhage.

Systemic toxicity with parenchymatous organs damage in bipyridyl herbicides poisoning is attributed to their oxidation and reduction in a cycling manner. This process leads to the production of superoxide anion and other free radicals, resulting in the chain reactions that damage cellular structures. Cells are additionally damaged due to depletion of NADPH that is consumed during redox cycling and detoxification of free radicals. Being the site of intensive energetic metabolism, the heart may be among the most sensitive target organs. The results of recent clinical study on patients with paraquat and/or diquat poisoning indicate that marked imbalance between increased oxygen demand and decreased oxygen supply because of myocardial depression, was a possible cause of death in circulatory failure. We believe that in the presented cases of diquat poisoning, primary cardiocirculatory disturbances led to fatal complications, heart and brain infarction.

Since the immediate measures to reduce the further diquat absorption and to enhance elimination by hemoperfusion, as well as administration of antioxidants, were not beneficial for survival in most cases of severe diquat poisoning, supportive care and symptomatic treatment in intensive care unit remains the mainstream therapy.

Conclusion

Clinical picture of diquat poisoning has been described in detail in a small number of cases. Local corrosive lesions, and systemic manifestations including severe gastroenteritis, acute renal failure, early development of bronchopneumonia, and signs of liver damage have been recognized. In all available reports, marked cardiocirculatory disturbances have been noticed, but there have been no reports on myocardial infarction, which we proved in the presented patients. We pointed out the heart as one of the most severely affected organs in diquat poisoning.

References


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