

Acute colchicine intoxication complicated with complete AV block

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Colchicine, is an old and well-known drug, used for treatment of rheumatic diseases. Nausea, vomiting, abdominal pain, and diarrhea are the clinical symptoms of colchicine poisoning. Cardiotoxicity can lead to mortality. We report a case of colchicine intoxication complicated with complete heart block. A 9-year-old patient ingesting colchicine 0.4-0.5 mg/kg was transferred because of elevation of liver enzymes, and deterioration of kidney functions and cytopenia. History of colchicine ingestion had been unknown at time of admission. After initial fluid and electrolyte treatment electrolyte imbalance ameliorated but kidney and liver functions worsened. In the third day of admission (7th day of ingestion), she confessed taking colchicine pills. Her state of consciousness became comatose and endotracheal intubation required. She developed complete heart block requiring temporary transvenous pacemaker implantation in the fifth day of admission. One day after pacemaker implantation, cardiopulmonary arrest developed again and remained completely unresponsive to CPR, and died. Cardiotoxicity of colchicine is leading cause of mortality. Tachycardia and conduction anomalies are not rare, but complete AV block in pediatric patient has never been reported. Although underlying mechanism is not known colchicine may have a direct toxic effect on conduction.

Key words: AV block, colchicine, toxicity.

Colchicine, is an old and well-known drug derived from *Colchium autumnale*, used for treatment for gout, Behcet's disease, and familial Mediterranean fever (FMF), sarcoidosis, and psoriasis¹. Colchicine toxicity is uncommon but with the widespread use of colchicine the number of cases has been increased. Intoxication develops after ingestion of high doses or even therapeutic doses. Ingestion more than 0.5 mg/kg of doses leads to major toxicity with 10% of mortality, over 0.8 mg/kg dose leads to increase in mortality to 100%². Death usually occurs as a result of hemodynamic collapse, central nervous system toxicity, or cardiopulmonary failure. Colchicine may have a direct toxic effect on cardiac impulse generation and conduction³. Here we report a case of colchicine poisoning complicated with complete AV block.

Case Report

A 9-year-old female patient attempted suicide by ingesting colchicine 0.5 mg/kg was transferred from local hospital 4 days after beginning of nausea and vomiting. She was transferred because of elevation of liver enzymes, and deterioration of kidney functions and cytopenia. History of colchicine ingestion had been not known at time of admission. Macrophage activation syndrome was the suspected diagnosis of patient. She was conscious but had pale and cold skin, and was hypotensive (blood pressure of 76/45 mmHg), capillary refilling time was prolonged. No pathological physical examination finding were detected. Laboratory studies were: white blood cells (WBC), 9600/ μ L; hemoglobin, 13.6 g/dl; platelets, 57000/ mm^3 ; aspartate aminotransferase, 630 U/L; alanine aminotransferase, 52 U/L; sodium, 129

mmol/L; potassium, 3.3 mmol/L; calcium, 6.1 mmol/L; lactate dehydrogenase, 5329 IU/L; D-dimer, 5250 ng/L; international normalized ratio, 3.26; activated partial thromboplastin time, 56.9 seconds; blood urea nitrogen, 41 mg/dl; serum creatinine, 1.27 mg/dl. Blood gas values were: pH: 7.45; partial pressure of carbon dioxide, 25 mmHg; bicarbonate, 17 mmol/L; base excess, -6.1 mmol/L. Fluid resuscitation started immediately, in short time period inotropic agents started. Echocardiography revealed normal systolic function of the left ventricle, with an ejection fraction of 60% and shortening fraction of 30%. After initial fluid and electrolyte treatment electrolyte imbalance ameliorated. Within two days neutropenia developed (absolute WBC, 200/ μ L) and thrombocytopenia 17000/ mm^3 worsened. In the third day of admission, she confessed taking colchicine pills. Her state of consciousness became comatose with a Glaskow coma score of 10 and endotracheal intubation required. Hypotension became more prominent and echocardiography revealed impaired systolic functions and she developed complete heart block in the fifth day of admission (Fig. 1). Long time pauses requiring resuscitation lead to temporary transvenous pacemaker implantation. One day after pacemaker implantation, cardiopulmonary arrest developed again and patient remained completely unresponsive to resuscitation, and died.

Discussion

Colchicine, is an old and well-known drug used for treatment for gout, Behcet's disease, and FMF, sarcoidosis, psoriasis¹. Although colchicine intoxication is rare, it is more common in countries where FMF is common. Major toxicity of colchicine leads to mortality.

Colchicine binds to the intracellular protein tubulin. In toxic doses, colchicine arrests mitosis. The systems with the highest turnover rate, bone marrow, gastrointestinal tract, and hair follicles, are the most vulnerable⁴. Colchicine also have a direct toxic action on myocardial cells. This effect may be related to binding of the drug to microtubules in myocytes, which interferes with cardiac conduction and contractility^{3,4}.

The clinical course of acute colchicine poisoning overlaps in three phases. After

ingestion within first 24 hours, gastrointestinal symptoms develop. The second phase multi organ involvement is common. Respiratory distress, cardiac arrhythmias, failure, arrest, encephalopathy, convulsions, renal failure, liver failure, disseminated intravascular coagulation, bone marrow suppression, hemolysis, metabolic derangements, myopathy, neuropathy, secondary sepsis can be observed in the second phase of intoxication. If patient survives, recovery and resolution of organ failure can be observed in 3–4 weeks after ingestion of colchicine⁵.

The main treatment of colchicine intoxication is supportive therapy. Fluid resuscitation, rehydration and inotropic support is mainstay of initial management. Treatment also includes correction of electrolyte and acid–base imbalance, antiarrhythmics, and mechanical ventilation. Temporary pacing may help patients complicated with complete heart block. Blood products, granulocyte colony-stimulating factor should be considered in patients with cytopenia and disseminated intravascular coagulation^{4,6}. Hemodialysis can be performed in patients with renal failure but not for elimination of drug due to rapid and extensive diffusion into all tissues shortly after oral administration, and large volume of distribution. Leukopheresis along with plasma exchange, or whole blood exchange can be performed in patient shortly after ingestion. In severe intoxication with 0.9 mg/kg colchicine whole blood exchange performed in early hours of ingestion may lead to increase in survival⁷. Immunotherapy by using colchicine-specific antibodies as used in digitalis toxicity, may have efficacy on treatment but unfortunately colchicine-specific Fab fragments are no more commercially available in Europe⁸. Extra corporeal life support is indicated in patients when acute

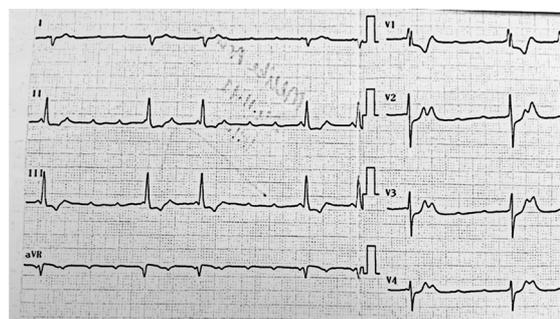


Fig 1. ECG of the patient at fifth day of admission.

heart failure caused by toxic myocarditis are not responding to conventional treatments. Although it is an invasive technique, having potential risks, it should be considered early in the management of such patients⁹. Early intervention, leukopheresis or whole blood exchange is the only predictor of mortality in patients with major colchicine intoxication.

Cardiotoxicity of colchicine is reported as leading cause of mortality. Tachycardia and conduction anomalies are not rare, but complete AV block in pediatric patient has never been reported. In this case, AV blockage occurred in 9th day of colchicine ingestion. AV block and myocardial involvement occurred almost simultaneously. In an animal model cardiotoxic effects of colchicine is reported as decrease in sarcoplasmic reticulum function and calcium myofilament sensitivity is responsible for the cardiotoxicity¹⁰. Although underlying mechanism is not known, colchicine may have a direct toxic effect on cardiac impulse generation and conduction as speculated by Mendis et al³. Temporary transvenous pacemakers as a part of supportive therapy may be lifesaving in patients with conduction system involved only. Due to depression of impulse conduction and myocardial excitability, myocardial response could not be observed few hours after the temporary pacemaker implantation. Unfortunately pacing did not change the outcome in this case.

Although cardiotoxicity is not rare as a result of major intoxication, there is no reported case of complete heart block associated with colchicine intoxication. Patients with colchicine intoxication complicated with complete heart block should be treated as the other patients with heart block, but in patients with myocardial involvement developed outcome of pacing is poor.

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