

Acute Angioedema in Paraphenylenediamine Poisoning

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Paraphenylenediamine (PPD), a derivative of paranitroaniline is widely used as an oxidisable hair dye. in dying furs and in photochemical and tyre vulcanizing industries.^{1,2} It is also commonly mixed with henna (leaves of lawsonia alba) in Africa, Middle East and Indian subcontinent, which is traditionally applied to color palms of hands, soles and feet and to dye hair a dark red shade.³⁻⁵ PPD causes contact dermatitis in susceptible individuals⁶, but when ingested, it causes acute angioedema of face and neck rhabdomyolysis and acute renal failure.¹⁻⁵ A case report is presented of a para-suicidal PPD poisoning following ingestion of a hair dye.

Case Report

A 14 year old African female was referred to the Department of Oral and Maxillofacial Surgery. King Fahad General Hospital. al-Medina Al-Munawwara, Saudi Arabia from the emergency department with acute progressive orofacial swelling of 3-4 hours duration. Initial history did not reveal any underlying medical cause, allergy, exposure or ingestion of any unusual substance, i.e. food or drug. Her pulse was 120/minute, blood pressure 110/60 and respiratory rate 28/minute. The patient had non-tender, non-pitting oedema of bilateral submandibular and submental areas. The edematous floor of the mouth was raised above the mandibular occlusal level and the swollen tongue was pushed against the palate. She was able to maintain her airway and tracheostomy was not considered essential. A diagnosis of acute angioedema was made. Intravenous hydrocortisone sodium succinate 200mg (Solu Cortef, Upjohn s.a. Puurs, Belgium) and oral Chlorpheniramine maleate 4mg (Histop, SPIMACO, Qassim, Saudi Arabia) were administered. The patient was admitted in the intensive care unit for close monitoring of the airway. Subsequently the patient was also noted to have rigidity, tenderness and painful movements of both the lower limbs, as well as, hoarseness of the voice. Routine blood tests showed the following abnormal values: white cell count $25 \times 10^9/l$. Glucose 15.2 mmol/l. Potassium 5.8 mmol/l, Creatinine Kinase (CK) 4380u/l, Aspartate aminotransferase (AST) 1455u/l. Alanine aminotransferase (ALT) 246 u/l and creatinine 200mg/dl. Arterial blood gases (pH 7.34, PO₂ 84.5 mm Hg, PCO₂ 29.3 mmHg, SO₂ 84.5% and HCO₃ 15.8mmol/l) showed mild metabolic acidosis. Urinalysis showed coffee brown urine which tested positive for blood, myoglobin and protein. On further interrogation it was revealed that patient had ingested some non-branded hair dye: solid sample of which were obtained from the patient's home. Blood, urine and solid sample of the ingested material were found to be positive for paraphenylenediamine using chemical spot test and thin layer chromatography. A diagnosis of acute PPD poisoning with orofacial angioedema, rhabdomyolysis, acute liver and renal impairment was made. Patient was given symptomatic and supportive therapy of intravenous 100mg methyl prednisolone (Depo Medrol, Upjohn s.a. Puurs. Belgium) 6 hourly, oral 4mg chlorpheniramine maleate (Histop, SPIMACO, Qassim, Saudi Arabia) 8 hourly and oral

20 mg. Frusemide (Diurex, Arab Pharmaceutical Manufacturing Co. Ltd. Suit, Jordan) 8 hourly. Patient's oro-facial swelling resolved to a great extent within 24 hours. Methyl prednisolone was tapered over three days after the resolution of edema. Her hemoglobin dropped from 11.3 g/dl at admission to 8.1 g/dl four days after admission. Endoscopy of Gastrointestinal tract, carried out because of difficulty in swallowing, showed congestive oesophagitis and diffuse hemorrhagic gastritis. Cimetidine 200mg (Timet. Aegis Ltd, Nicosia, Cyprus) was given orally for two days. Patient's general condition, neurological status and laboratory parameters progressively improved. She was discharged from the hospital 15 days after admission and was prescribed oral Frusemide 20 mg 8 hourly. Three months follow-up showed complete resolution of all the symptoms and all the medications were discontinued.

Discussion

Paraphenylenediamine (PPD) is a derivative of paranitroaniline.¹ Complex reaction takes place and several intermediates are produced on oxidation of PPD. However, the major product formed is Bondrowski's base which is allergenic, mutagenic and highly toxic.² First case of PPD poisoning was reported in a hairdresser in 1924 following exposure due to PPD dye handling.⁷ PPD is readily absorbed on dermal contact.⁶ Six children in a series of 31 Sudanese children with PPD poisoning were reported not to have ingested hair dye. An Arab lady developed acute life threatening pulmonary edema after she had painted one hand with a henna mixture.³ The symptoms are considered to be dose related and patients with ingestion of larger amounts of PPD have higher morbidity and mortality.² Onset of symptoms after ingestion of the dye is about 4-6 hours. The patients with PPD poisoning have characteristic angioedema of face and neck on initial presentation.^{2,4,5} The patient has marked oro-facial swelling with swollen hard protruding tongue and edematous bull neck. The patient may have difficulty in breathing secondary to upper respiratory tract edema. The above facial features along with characteristic chocolate brown colour of the urine could be a confirmative evidence of PPD poisoning in the absence of laboratory facilities and when history is lacking in case of emergency.⁵ Other consistent features are rigidity and tenderness of limbs secondary to rhabdomyolysis; and acute renal failure.⁸ Other reported features are leukocytosis, anaemia secondary to hemolysis, haemoglobinuria and haemoglobinuria. Toxic features include methemoglobinemia, gastritis, hoarseness of voice, cardiac toxicity, hepatitis, convulsions, coma and sudden cardiac death.^{1,2} Exophthalmos and blindness were reported in one case. Hypotensive shock is recognized and is associated with poor prognosis. Four deaths in a series of 18 patients have been reported due to acute airway obstruction (one patient), acute renal failure (two patients) and sudden cardiac arrest (one patient). The major early challenge to life is asphyxia and renal failure at later stages.⁵ There is no specific antidote available for PPD. Treatment is mainly symptomatic and supportive depending on the state of presentation. Haemodialysis is life saving when oliguria develops. Early clinical diagnosis and therapeutic intervention is essential if full recovery is to be expected.² Angioedema is a well-recognized non-pitting edema involving the deeper layers of the skin, subcutaneous tissue, and mucosa that can lead to life threatening airway obstruction.¹⁰ Angioedema can be hereditary or acquired. Acquired angioedema includes

non-hereditary CI-estrase inhibitor deficiency; idiopathic, allergic, and drug induced forms; angioedema associated with lupus erythematosus and hypereosinophilia; and angioedema caused by physical stimuli.¹¹ A characteristic oedema of head and neck was produced experimentally in rabbits and cats by intraperitoneal injection of PPD HCl.¹² Repeated PPD dermal applications in Guinea Pigs showed increase in histamine suggesting allergic or hypersensitive reaction associated with the increased permeability of mast cells.⁶ Mild airway obstruction were managed by steroids and antihistamine medications in a series of 18 patients. In more serious cases airway was secured by tracheostomy. Sixty five percent of the patients in the series required tracheostomy.⁵ Ishoo et al¹³ in a retrospective review of 81 angioedema patients suggested an airway management staging system based on anatomic site of presentation. Patients with facial rash, facial edema, lip edema (stage I), and soft palate edema (stage II) were treated as outpatients and on the hospital ward. Patients with lingual edema (stage III) usually required ICU admission. All patients with laryngeal edema (stage IV) were admitted to ICU. Airway intervention was necessary in 7% of stage III and 24% of stage IV patients. Timely decision regarding the airway management is vital as endotracheal intubation becomes almost impossible once edema develops in serious cases.⁵ Toxic effects of PPD are considered to be related with higher doses causing rhabdomyolysis, acute renal failure and an increased likelihood of sudden cardiac death.² Skeletal and cardiac muscle necrosis was experimentally induced by N-methylated PPD in rats.¹⁴ Scattered coagulation necrosis of skeletal muscles was shown in autopsies.^{2,9} Increased free radical formation in PPD poisoning causes histopathologically demonstrated tissue damage in guinea pigs.⁶ Passing of chocolate brown urine and acute renal failure is another consistent feature of PPD poisoning. Hemolysis, methemoglobinemia and direct toxic action of the chemical or its metabolic products on the renal parenchyma are suggested to be the most likely factors leading to acute renal failure.^{1,2} The metabolic products of PPD have a high urinary excretion rate, and their oxidation produces quinone-diamine, which is a potentially nephrotoxic substance.² Autopsy of patients revealed renal tubular occlusion due to myoglobin casts with histological evidence of acute tubular necrosis.²⁹ Myoglobin casts released due to rhabdomyolysis might be an additional factor contributing to renal failure.¹⁵ Renal dialysis is life saving when oliguria develops.¹² Early diagnosis of PPD poisoning can be made on the basis of its characteristic presentation. Medical treatment with steroid and antihistamine should be commenced. Airway should be closely monitored and maintenance of airway patency should be ensured with timely endotracheal intubation or tracheostomy. Renal dialysis should be carried out if patient develops oliguria. Most of the reports about PPD poisoning have been reported in Africa and Asia, and its importance needs to be highlighted further in view of use of henna with additives in our culture.²

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