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Ethylene Imine Poisoning. A Case Report

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Abstract. A case is described of accidental inhalation of ethylene imine vapour in a chemical worker. This resulted in glottic oedema which required tracheostomy. Artificial respiration was needed because of failure to maintain adequate arterial oxygen levels. The patient developed profuse salivation and sputum production. Endoscopy showed that the mucosal surfaces of the pharynx, trachea and major bronchi were destroyed. The patient was treated with steroids and antibiotics for pulmonary infection. Recovery was slow but he was eventually able to leave hospital. He was later re-admitted with recurrent infection and developed acute airway obstruction from which he died.

Post-mortem examination showed extensive destruction of the mucosal lining with erosion and collapse of the cartilages. This was the cause of death.

Previous reports of ethylene imine poisoning are reviewed. This appears to be the third fatal case.

Key words: Poisoning, Ethylene imine, Industrial injury, Artificial respiration, Tracheostomy, Glottic oedema, Airway obstruction, Pulmonary infection.

Introduction

Ethylene imine (Ch_2CH_2NH) is a highly reactive volatile liquid widely used in the chemical industry in a number of organic syntheses, and in the manufacture of paper and textiles. It is highly inflammable, explosive if exposed to air, corrosive to most metals and glass, and a powerful tissue poison. It is an alkylating agent and is known to be extremely toxic by ingestion, inhalation or by skin contact.

Reports from Germany (10) and America (11) have described skin burns and damage to mucous membranes involving respiratory and alimentary tracts, and to the eye. Transient albuminuria and liver function abnormalities have also been detected. There have been no previously published reports of cases in this country. The patient described here suffered acute poisoning, and initially responded well to treatment, but died later from an unforeseen complication.

Case Description

The patient was a previously fit, 53 year old storekeeper in a chemical factory. In the afternoon of July 5th 1973, he was transferring ethylene imine between two containers. His gas mask did not fit properly and permitted inhalation of the vaporised substance over a period of approximately 30 minutes. On admission to Addenbrooke's Hospital, within an hour of inhalation, he had developed irritation and watering of the eyes, nasal congestion with profuse discharges and bouts of sneezing, and difficulty in talking and swallowing. He had vomited several times, and complained of feeling breathless. On examination, he was distressed, with watering reddened eyes and profuse nasal and salivary secretions which he was unable to swallow. He was dyspnoeic with a respiratory rate of 35–40 breaths per minute. Although his colour was normal he had coarse crepitations at the left lung base, and these were shortly detectable over all the lung fields. At that time he was still able to talk, but fifteen minutes later he was unable to phonate and breathing became even more difficult. It was obvious that he was developing severe respiratory obstruction.

Table 1. Arterial blood gases referred to in the text

Date	H+concn. mmol/1	$PaCO_2$ kPa	PaO_2	Standard Bicarbonate mmol/1	Base Excess mmol/1	FIO_2
5th July	26	5.2	8.0	36	+14	0.7
6th July	29	4.3	13.8	28	+5	0.6
30th August	37	6.0	10.2	27	+6	0.2

The patient was therefore intubated using general anaesthesia consisting of 50% nitrous oxide, oxygen and halothane. Laryngoscopy revealed swelling and distortion of the pharyngeal mucosa, uvula, and epiglottis. The laryngeal oedema was so severe that the glottis was barely visible and would allow the passage of an endotracheal tube no larger than 7 mm. Within a few minutes of intubation, acute pulmonary oedema developed and at the same time a copious fluid stool was passed. An intravenous infusion was set up and frusemide 40 mg and hydrocortisone 200 mg given intravenously. The patient was ventilated with oxygen-enriched air using an Ambu bag. He was transferred to the Intensive Care Unit where artificial respiration was continued with an Air Shields ventilator. An inspired oxygen concentration of 70% was necessary to prevent cyanosis. Sedation was achieved using phenoperidine. Frequent tracheal suction was required, and nasal and salivary secretions were still profuse. Pulse and blood pressure were stable. Arterial blood gases on the day of admission are shown in Table 1. The haemoglobin was 14.69 per d/l and white blood cells 16,000 per cu.mm. Serum urea, electrolytes and liver function tests were normal. An electrocardiogram showed sinus rhythm, with right bundle branch block which persisted during his stay.

A chest X-ray revealed severe pulmonary oedema. An inspired oxygen concentration of 100% was needed to maintain a PaO_2 of 8.0 kPa. Drug treatment consisted of hydrocortisone sodium succinate 200 mg 6 hourly, ampicillin 500 mg 6 hourly and frusemide. Initially, intravenous fluids with potassium supplements were given. Urine output was adequate. The cardiovascular system remained stable overnight and there was no further diarrhoea.

The next morning, July 6th, the patient's clinical state was little different except that he had developed marked facial oedema. He remained alkalaemic although oxygenation was satisfactory (see Table 1). An attempt was made to let him breath spontaneously for a short time but he became dypsnoeic with periods of apnoea. Long term ventilation was obviously indicated and tracheostomy was therefore performed at 14.00 hours under general anaesthesia consisting of nitrous oxide, oxygen and phenoperidine. Laryngoscopy at the time revealed the same appearances as before, except that the pharyngeal mucosa was by now starting to slough. A 39 F tracheostomy tube was inserted through a stoma at the level of the third tracheal ring.

Nasal and tracheal secretions were still profuse and suction was necessary at 15 minute intervals. Over the next two days the volume of secretions had lessened, the pulmonary oedema diminished and on the fourth day after admission the PaO_2 was 13.3 kPa on 50% inspired oxygen. Artificial ventilation with air produced a PaO_2 of only 5.8 kPa. A week after admission he was still on continuous artificial respiration, but by this time 30% oxygen was sufficient to maintain his PaO_2 at 13–17 kPa. The metabolic alkalosis had now resolved. Chest auscultation was normal and the amount of tracheal and bronchial secretions was now slight. A programme of weaning from the ventilator was therefore begun, using an ultrasonic nebuliser to humidify the inspired oxygen-enriched air during the periods of spontaneous respiration. The dosage of steroids was gradually reduced. The weaning process was slow and by the 11th day the patient still only managed an hour off the ventilator before becoming exhausted. At this time the pharyngeal mucosa showed signs of healing although there was still some slough present.

Thirteen days after admission the patient developed a fever and produced purulent sputum which grew staphylococcus pyogenes and pseudomonas pyocyaneus, and he was therefore treated with colistin and cloxacillin. By day 24 he was off the ventilator throughout the daytime. His vital capacity was by then 0.5 litres. By day 26 the patient was completely weaned and was able to walk around the ward. A silver tracheostomy tube with a speaking flap was therefore inserted. This was in turn removed on day 32 and the wound allowed to granulate over.

On the 8th August, when the patient was discharged from hospital, his lung fields were clear and he was producing no sputum. Chest X-rays showed accentuated lung markings in both fields. No other abnormality was detectable and in particular there was no evidence of tracheal stenosis. However, his vital capacity was only 2 litres with an FEV_1 of 1.4 litres (70%). He returned home, taking prednisone 2.5 mg daily, but this was tailed off over the next two weeks.

The patient was re-admitted to hospital on 30th August with a two-day history of a dry cough and shortness of breath even on mild exertion. He was dypsnoeic at rest with signs of increased inspiratory effort. Widespread rhonchi and wheezing were audible in all lung fields. A chest X-ray showed a normal heart with accentuation of lung markings in both lower zones. He was treated with salbutamol and steroids. Vital capacity at this time was 2 litres with an FEV_1 of 0.8 litres (40%); there was no improvement after giving a broncho-dilator. Arterial blood gases showed him to be hypoxic while breathing air (see Table 1). Sputum culture again demonstrated staphylococcus pyogenes and pseudomonas pyocyaneus and he was treated with colistin and cloxacillin.

Tomograms of the trachea showed an apparent stenosis in the form of lateral narrowing at the level of the sternal notch. Direct laryngoscopy and bronchoscopy performed by Wilsdon on the 4th September showed the tracheal lumen narrowing to a lunate slit in the sagittal plane, 15 cm from the upper incisors. The left side was apparently fixed and epithelialized but the right side was mobile and ulcerated. The attacks of dyspnoea lessened in frequency and severity and the infection subsided with treatment. On 15th September the patient was examined by a thoracic surgeon who agreed to perform a segmental resection of the trachea when the infection had completely cleared.

On 16th September in the early hours of the morning, he suddenly became severely dyspnoeic and cyanosed. He was immediately taken from the ward to the operating theatre and the tracheostomy re-opened, a cuffed tracheostomy tube inserted and the lungs ventilated artificially. He was sent back to the I.C.U. where attempts at resuscitation were continued. Despite the use of increasing concentrations of oxygen, it proved impossible to maintain adequate arterial oxygenation. His arterial pressure fell progressively and after two hours his heart arrested and he died.

Post-mortem Findings

Autopsy was performed by Gresham (3).

The most remarkable findings were in the respiratory system. The tracheal mucosa was absent and its gross appearance was of horizontally purple bands of tissue separated by bare yellow cartilage. The major bronchi presented a similar appearance. The walls of the larger air passages were flexible and had collapsed to form slit-like lumina, although there was no organic tracheal stenosis. There was pus in the bronchi and bronchioles and some evidence of pulmonary oedema. The myocardium showed a few small fibrotic areas but there was no other cardiac abnormality.

The histological appearance of the lungs and air passages was strikingly abnormal. The mucosa was mostly replaced by granulation tissue, although there were also extensive areas of fibrosis. Much of the cartilage was eroded and kinked. Many smaller bronchi contained granulomatous polyps, sometimes entirely occluding the lumina. Areas of emphysema and broncho-pneumonia were widespread. The mediastinal lymph nodes contained sarcoid-like granulomata.

Discussion

This case showed many of the previously reported features of ethylene imine (EI) poisoning. Descriptions of 73 cases, collected between 1939 and 1964 from published reports and from the records of the Badische Anilin and Soda Fabrik, have been reviewed by Thiess (10); there were two fatalities. We believe the case described to be the third to end fatally.

After contact of liquid ethylene imine with the skin, erythema usually follows within a few minutes, often accompanied by blistering and skin necrosis. Attempts to prevent this by washing with water or dilute acetic acid (to neutralise the EI) are only partially successful, owing to the high solubility and rapid skin penetration of EI. The onset of these signs may be delayed for hours. Healing may also be delayed, sometimes taking many weeks and leaving a scar. Our patient had no direct skin contact with the liquid, although he developed facial oedema as a result of contact with the vapour.

More serious are the direct effects of ethylene imine vapour on the mucous membranes, particularly of the eyes and the upper respiratory tract. The first symptoms are lacrimation, rhinorrhoea, irritation or pain in the nose and throat, "dryness" of the throat, cough and dypsnoea. Prolonged kerato-conjunctivitis, resistant to treatment, was reported by Thiess, although the ultimate prognosis appears to be good. Reddening, swelling, punctate haemorrhages, oedema and ulceration of the nasal mucosa are common after inhalation and also last for several days. Nasal breathing may be impossible for a while. Both these organs were affected in our patient in whom mucosal reddening and discharge persisted for some days, but eventually recovered without ill effects.

The most serious effects of inhalation are on the mucosa of the pharynx, larynx and bronchial tree. The symptoms are profuse salivation, cough, hoarseness and difficulty in breathing and in swallowing. Nausea and vomiting are very common, even in patients without evidence of systemic absorption and may be the result of local irritation. Sloughing commonly follows, leaving raw ulcers which heal slowly. Oedema of the glottis, which was such a prominent feature of our case, has been seen in others. This is a life-threatening emergency, capable of causing early death if not treated promptly by endotracheal intubation. Acute pulmonary oedema occurring after the relief of respiratory obstruction, as we experienced, is not uncommon. We believe it may be due to further hypoxia resulting from apnoea following the sudden reduction of a raised arterial CO_2 tension in a patient who is already hypoxic. Tracheostomy may be performed at leisure once the airway has been secured by intubation.

The effects of inhaled ethylene imine on the bronchial mucosa must be presumed to be as described above. Râles in the lungs, sometimes accompanied by non-specific radiological changes were observed in several of Thiess' cases. In our patient they were prominent at an early stage, before respiratory obstruction occurred, and must have been precursors of the profuse pulmonary oedema which occurred after the obstruction was relieved. In some patients the râles clear after a few hours, while in others infection may supervene and progress to bronchopneumonia. This was the course of events in our patient, in whom the infection was never completely eradicated. Thiess has reported the coughing up of "pseudodiphtheritic" sloughs in a fatal case, although in none of his cases did death occur in the absence of evidence of systemic absorption of EI.

We consider that our patient's principal (and ultimately fatal) lesion was the destruction of the lining of his respiratory tract. Gresham and West (3) considered that the widespread destruction of cartilage was associated with extensive formation of granulation tissue. This would be expected to release proteases which erode cartilage. The process was probably delayed by the use of steroids

in the earlier stages of treatment. Regeneration of cartilage is in any case slow, usually taking many weeks. The changes in the affected cartilage resemble those found in chronic relapsing perichondritis, but in our case were limited to the tracheal cartilages (4). The mucosal destruction was greatest in the trachea and major bronchi. It may be significant that this was the area subjected to repeated tracheal suction. In view of the autopsy findings we suggest that death was due to extensive airway obstruction, with collapse of the larger bronchi and trachea. The tomographic appearance of the trachea was due to this collapse rather than to a true stenosis. It is not known what precipitated the final acute episode of respiratory obstruction.

The effects on the bronchial mucosa last a surprisingly long time. Weightman and Hoyle (11) described five students who inhaled EI, of whom four showed increased duration of forced expiration which in two cases had not returned to normal within three months. Our own patient showed a similar disability which did not improve after giving bronchodilator, confirming that the lesion is thickening of the bronchial walls rather than true bronchospasm. Thiess reported the use of artificial respiration in one patient, although the indication is given as respiratory paralysis. Our patient was artificially ventilated because of his inability to maintain a reasonable arterial oxygen tension.

Ethylene imine is highly soluble and there is strong evidence that not only it is rapidly absorbed into the body, but that it causes further damage therein. The route of absorption may be either via the skin or mucous membranes or via the lungs in the case of the vapour. Our patient showed a profound metabolic alkalosis during the first 24 hours, possibly due to the absorption of the very alkaline EI.

Symptoms of systemic absorption are hard to classify. Nausea and vomiting are also a feature of ethylene oxide poisoning and a central nervous mechanism for this has been postulated. However, most casualties seek medical aid because of local symptoms, although some of Thiess' patients complained of cramp-like abdominal pain. Our patient passed diarrhoea stools without pain, but whether this was due to systemic absorption or to swallowing saliva containing EI, we cannot say.

Animals painted with aqueous solution of EI on the skin or conjunctiva later died (7). Silver and McGrath (9) and Carpenter et al. (1) exposed mice to measured concentrations of EI and were able to show toxic effects at 10 ppm, the LD 50 being 4 mg per litre of air (for 10 minutes exposure). Applying EI to the skin of guinea pigs caused death from systemic absorption, the LD 50 varying from 0.07 ml/per kg body weight for 10% solution to 0.34 mg per kg for 1% solution. Animal studies have revealed a number of systemic effects. Erlich (1898, quoted by Thiess (10)) apparently showed a toxic action on the kidney; Thiess (10) quotes work undertaken in 1942 by I.G. Farben Industries (5) in which EI caused renal hyperaemia, papillary oedema and tubular necrosis. This was confirmed by Carpenter et al. (1) who demonstrated generalised visceral hyperaemia associated with lymphocytopenia and polymorphonucleosis.

There is well-documented evidence of systemic effects in humans. Weightman and Hoyle (11) observed transient polycythaemia, with a maximum haemoglobin concentration of 20 g per d/l, leucocytosis with up to 15,000 cells per cu.mm. eosinophilia and albuminuria. The polycythaemia presumably resulted from loss of extracellular fluid in the form of oedema as well as from external losses. All five of their cases had raised cephalin flocculation. A fatal case described by Thiess also had polycythaemia, albuminuria, haematuria and 28,500 white blood cells per cu.mm. Effects on the heart appear to be common in seriously intoxicated patients. One of Weightman and Hoyle's patients showed left axis deviation, right ventricular preponderance and T-wave reversion, on the E.C.G. Thiess also reported electrocardiographic changes consisting of partial right bundle branch block and signs of left ventricular injury in a patient who later died as a result of his second cardiac arrest. The other of his cases died from heart failure. Our patient also had persistant signs of right bundle branch block on the electrocardiogram.

There is no specific treatment for ethylene imine poisoning. The skin and mucosal lesions heal after 4–8 weeks and if supportive treatment is successful, there is a good chance of recovery, even in seriously intoxicated patients. Steroids have usually been given both topically and systemically. We believe that antibiotics should be reserved for the treatment of proven infections. Inotropic drugs may be required for the treatment of heart failure. Careful fluid and electrolyte management is essential in view of the initial haemoconcentration and the possibility of renal damage. Tracheostomy with or without artificial respiration may be needed for the aspiration of bronchial secretions and to maintain adequate oxygenation.

Ethylene imine is well recognised as a dangerous substance. The Dow Chemical Company state that "in the laboratory where relatively small amounts of ethylene imine are used, experience has shown that if all work is carried out in well designed and properly functioning hoods, ethylene imine can be safely handled" (3). They recommend that the vapour concentration in the atmosphere should be monitored continuously in working areas. Protection against skin contact should be ensured by use of protective clothing, chemical worker's goggles and if vapour is likely to be encountered, by an efficient gas mask (I.L.0.6). Our patient was wearing an ill-fitting gas mask which permitted vapour to come into contact with his face and to be inhaled.

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