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Severe Chlorate Poisoning: Report of a Case*, **

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Abstract. A case of severe sodium chlorate poisoning was observed within 5 h after suicidal ingestion of 150–200 g of the herbicide. Methaemoglobinaemia was the early symptom of the intoxication. Treatment with methylene blue and ascorbic acid could not prevent a massive haemolysis with disseminated intravascular coagulation. Hypercoagulation and hyperfibrinolysis could be treated successfully with exchange transfusions, heparin and fresh plasma. During the first hours, 70 mmol chlorate were excreted before complete renal failure occurred which required haemodialysis for several weeks. Clinical observations and in vitro experiments provide evidence that methylene blue is effective only in the very early stages of chlorate poisoning. Consequently, the following treatment is suggested: gastric lavage, exchange transfusion, bicarbonate infusion, haemodialysis, anticoagulation with heparin and substitution of clotting factors if necessary.

Key words: Sodium chlorate poisoning – Methaemoglobinaemia – Methylene blue – Haemolysis – Disseminated intravascular coagulation

Introduction

The formation of methaemoglobin (haemiglobin, MetHb) is a characteristic symptom of chlorate poisoning. The often fatal outcome, however, is rarely attributable to anoxaemia due to the lack of normal haemoglobin but rather to the haematological and renal complications which follow extensive haemolysis. Patients frequently are admitted to hospital very late (Mengele et al. 1969; Lee et al. 1970; Stavrou et al. 1978) and the early stages of poisoning are not observed. Some time after the intoxication, MetHb is observed only in the serum and not in the erythrocytes. This seems to be the reason for the view that is

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prevalent in the recent literature that in chlorate poisoning the oxidation of haemoglobin is preceded by haemolysis (Gordon and Brown 1947; Klendshoj et al. 1962; Knight et al. 1967; Mengele et al. 1969). However, O'Grady and Jarecsni (1971) described a patient who died 2 h after ingestion of chlorate with 80% methaemoglobin which was entirely within the red cells.

Methods

Chlorate was determined in frozen plasma and urine by modification of the method published by Pugh and Sheahan (1971): 0.5 ml samples were mixed with 0.8 ml 2-n sulfuric acid and 0.1 ml of 10% phosphotungstic acid (Folin and Wu 1919) to precipitate the protein. Chloride was determined amperometrically (chlor-o-counter, Fa. Marius, Utrecht, NL) in triplicate with 0.1 ml of the clear supernatant. To 0.8 ml supernatant a piece of metallic zinc (appr. 300 mg) was added and allowed to react at room temperature for 48 h during which reduction of chlorate to chloride was complete. Chloride was measured as before and the chlorate concentration calculated from the difference. Evaporation losses were corrected for by using standard solutions of 100 mM NaCl and $NaClO_3$, respectively.

MetHb was measured photometrically at 630 nm. The extinction difference between MetHb and MetHb-cyanide in the sample was compared to that of a sample that had previously been completely oxidized by ferricyanide.

Protein was determined by a biuret method according to Bode et al. (1968) using bovine serum albumin as a standard.

Case Report

A 26 year old housewife who had been hospitalized several times for depression and an attempted suicide was found by her husband in a cyanotic state. She had swallowed a commercially available herbicide ("Unkraut-Ex") dissolved in beer. The herbicide consists of 75% $NaClO_3$ and 25% NaCl. According to her husband, she had emptied a tin that contained approximately 250 g, which would correspond to 150–200 g of sodium chlorate. The maximal time that could have elapsed between ingestion and admission to hospital was 5 h (for convenience, all data will be related to the time of admission).

At that time, the patient was conscious and without apparent distress. She was deeply cyanotic. MetHb was nearly 50%, all other laboratory values (Table 1) were within the normal range. Blood smears showed a number of echinocytes which had filament-like connections. An extensive gastric lavage was immediately performed and methylene blue and ascorbic acid were given intravenously. Sodium bicarbonate was infused to keep the base excess above + 7 mM. During the first 2 h, the patient voided clear urine (Table 2). Later, the urine turned dark brown and became muddy. 70 mmol chlorate (= 7.4 g $NaClO_3$) were excreted before the production of urine subsided.

Chlorate measurements in frozen plasma were negative. This seems understandable, because due to the measurement by a difference method chlorate values lower than about 5 mM would not be detectable.

After 14 h, total haemoglobin had changed only by 10%, while the erythrocyte count was dramatically decreased from 4.7 million/µl to 2.4 million indicating that more than 40% of the cells were haemolysed (Fig. 1). On admission, the serum was of normal colour. After 14 h, serum electrophoresis showed a large peak in the globulin α_2-β-region comprising 45% of total protein. A decrease of the thrombocyte count indicated an intravascular coagulation which was confirmed by the measurement of coagulation factors (Table 3). Fibrin degradation products showed a massive increase whereas plasminogen was a below the normal limit demonstrating hyperfibrinolysis as well. Anticoagulation with heparin was begun and an exchange transfusion with 6.5 l of blood took place 16 h after admission. Due to a number of unfortunate circumstances outside the hospital blood of the patient's blood group (B) was not available earlier. Simultaneously, haemodialysis was started. On

Table 1. Laboratory values on admission

Red cell count	$4.7 \cdot 10^6/\mu l$
Haemoglobin	14.4 g/100 ml
Packed cell volume	44%
White cell count	9,500 µl
Platelet count	322,000 µl
Serum sodium	153 mM
Serum potassium	4.2 mM
pO_2	94.5 mm Hg
pCO_2	37.4 mm Hg
pH	7.40
Base excess	− 1.5 mM

Table 2. Renal function after chlorate poisoning

	Time after admission				
	1–3 h	3–5 h	5–7 h	7–9 h	9–11 h
Urine volume (ml)	750	250	35	20	15
Protein (mg/ml)	–	4	7	15	25
Chloride (mM)	101	102	101	71	70
Chlorate (mM)	86	24	18	10	5

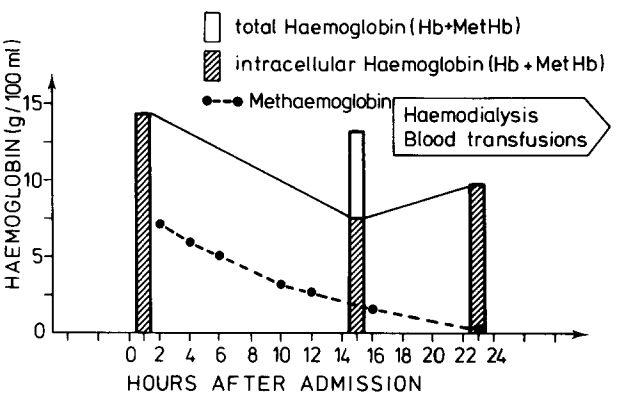

Fig. 1. Haemoglobin values after sodium chlorate ingestion. The decrease in total methaemoglobin content indicates methaemoglobin destruction to haematin, which is not measured by the method used, rather than reduction to functional haemoglobin. Free haemoglobin is completely cleared 5 h after beginning of haemodialysis

the following day, bleeding from old venous punctures was observed as well as epistaxis and a haematoma of the abdominal wall. Symptoms of ileus developed and an intraabdominal haematoma was verified sonographically. These complications could be treated successfully with fresh plasma and heparin.

Blood gases, which were normal on admission (Table 1), showed a continuous deterioration: pO_2 went down to 40 mm Hg after 24 h despite of oxygen administration (pCO_2 = 51 mm Hg) necessitating intubation and artificial respiration, which had to be continued intermittently for 6 weeks. During this period, several attacks of pneumonia complicated the clinical course.

The leucocyte count rose to 38,000/µl after 14 h and remained elevated for 10 weeks. After the initial decrease, the number of thrombocytes increased steadily. Normal values were measured on day 11; on day 29 1.15 million/µl were attained. Throughout the whole observation period, the platelet count remained elevated (> 0.6 million/µl).

Table 3. Coagulation disturbances after chlorate poisoning

	Normal values	Time after admission		
		16 h	40 h	17 days
Platelets	140–440 · $10^3/\mu l$	48	110	357
Fibrinogen	2–4 g/l	2.7	4.0	6.3
Factor V	60–120%	32	49	88
Factor VIII	70–120%	10	90	100
Plasminogen	100–200 mg/l	54	30	84
Fibrin degradation products	80 mg/l	5,120	1,280	160
Antithrombin III	180–310 mg/l	150	170	256
ELP (elastase-like-protease)	∅ mg/l	446	4	449

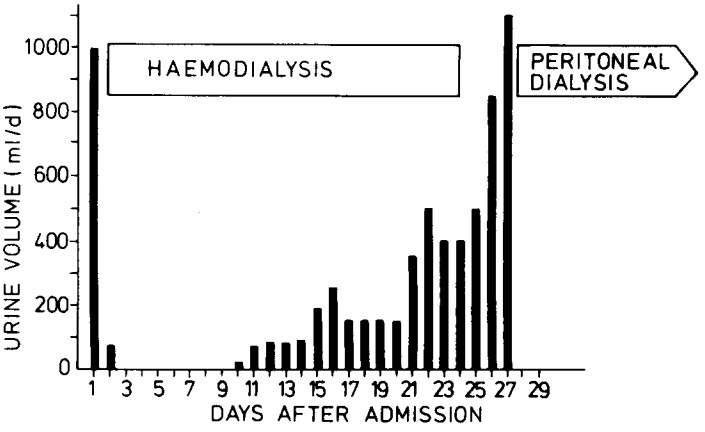

Fig. 2. Renal failure after sodium chlorate ingestion. Renal function ceased completely within 12 h and recovered slowly requiring 4 weeks of haemodialysis and 2 weeks of peritoneal dialysis

Liver function was only moderately disturbed. Serum transaminases were elevated during the first 10 days (maxima: SGOT 260, SGPT 180 U/l on day 3). Bilirubin was only slightly elevated (< 1.8 mg/100 ml) for 3 weeks.

Renal function was completely absent for 10 days and recovered only slowly (Fig. 2). Peritoneal dialysis could be discontinued after 40 days and the patient was discharged 3 months after admission. Creatinine remained elevated to 1.8 mg/100 ml serum and urea was 46 mg/100 ml.

Discussion

Chlorates have been used extensively in medical therapy throughout the last century and even longer as a local disinfectant in gargles and toothpastes. More than twenty fatal intoxications were collected from the literature between 1879 and 1886 by Marchand (1887). More recently, medical intoxications are a result of confoundation of chloride (e.g., Natrium chloratum) with chlorate (Natrium chloricum; Cochrane and Smith 1940; Klendshoj et al. 1962; Lee et al. 1970).

More often, sodium chlorate is ingested deliberately. Accidental poisoning with herbicidal preparations is rare (Stavrou et al. 1978). One of the characteristic features of chlorate poisoning is the great variability in the toxic effects. In some instances, a few grams cause serious intoxications (Stavrou et al. 1978); other patients survive massive doses. Stokvis (1886) was misled by experiments in rabbits which tolerate chlorate very well and stated that "sodium chlorate is not more and not less toxic than plain kitchen salt". At the same time, Hayem (1886) classified the chlorates as a special group amongst the methaemoglobin-forming agents as they form MetHb only after prolonged contact with erythrocytes, which are destroyed at higher chlorate concentrations (Cochrane and Smith 1940).

The case we observed confirms this observation. Five hours after admission, the only pathological finding was methaemoglobinaemia. Some hours later, haemolysis followed. The life-threatening disseminated intravascular coagulation and the renal failure may be regarded as a consequence of haemolysis. Haemolysed red blood cells (ghosts) have coagulating properties similar to platelets (Bradlow 1961). A direct effect of chlorate on thrombocytes, however, cannot be excluded. But on the other hand, fibrinolysis can also be activated by haemolysed erythrocytes (Künzer and Haberhausen 1963). Lee et al. (1970) observed an extremely shortened survival of platelets 7 days after the intoxication ($t_{1/2}$ was 5 h instead of 5 days).

The saturation of the reticuloendothelial system (RES) by waste products of the haemolysis causes a reduced clearance of fibrin degradation products and activated clotting factors thus aggravating the coagulation disorder. Brandslund et al. (1980) explained the severity of haemorrhagic diathesis in two cases of haemolytic uremic syndrome in penicillin-induced serum thickness as a consequence of an excessive workload of the RES. The appearance of elastase-like protease (ELP) in the plasma of our patient indicates an involvement of the neutrophil granulocytes in the pathogenesis of the heavy bleeding. It is known that ELP and other proteases released from the neutrophils degrade fibrinogen and the coagulation factors II, V, VII, VIII, XII, and XIII (Egbring and Havemann 1978). Whether the release of ELP is a consequence of enhanced phagocytosis or of direct damage of the neutrophils caused by chlorate is unclear, but the increase of the leucocyte count rather indicates an increased activity. The continuing intravascular coagulation was probably the reason for the failure of blood transfusions to raise the haematocrit in the case described by Gordon and Brown (1947). The lysed cells are sometimes observed in the circulating blood before they are phagocytised by macrophages (Bloxham et al. 1979) or taken up by the liver (hepatocytes and Kupffer cells are filled with brown pigment, Gordon and Brown 1947) and by the spleen. Marchand (1887) reported that in nearly all cases an enlargement of the spleen was seen. The blocking of the RES could also contribute to the haematological complications by inhibiting the clearance of proteases and explain the longlasting increase of the thrombocyte count after the acute phase of the intoxication. It seems that the haemoglobin is to a great extent destroyed by chlorate as the massive haemolysis does not lead to a significant increase of serum bilirubin. The trapping of red cells in the spleen indicates a more profound

alteration of the erythrocytes than merely the oxidation of haemoglobin. Membrane changes are likely to decrease the flexibility of the erythrocytes and their exposition to mechanical stress during the passage through the lineal meshwork is likely to rupture the membrane.

Renal failure may be caused by methaemoglobinuria alone (Bing 1943) or by a combination with a direct toxic effect on the proximal tubule (Oliver et al. 1951). In addition there is a correspondence of the clinical features of the haemolytic uraemic syndrome (Clarkson et al. 1970), which leads to characteristic histological alterations of the kidneys (fibrin deposition in afferent arterioles and glomerular capillaries, often causing trapping of red cells and platelets and occlusion of the affected vessels. As Bing (1944) has shown that acidosis is an important factor in the development of the renal lesion, the infusion of sodium bicarbonate is recommended. It has the additional advantage that the formation of MetHb is slower in an alkaline medium (v. Mering 1885; Mayer 1922).

Incubations of human red blood cells with chlorate and nitrite demonstrate important differences in the formation of MetHb. Nitrite transforms essentially all Hb into MetHb within a few minutes (Fig. 3a). Washing of the cells and incubation with methylene blue leads to a reduction of MetHb. Chlorate forms MetHb only after prolonged exposure and this change can only be reversed in the early phase of the experiment (Fig. 3b). When the degree of oxidation is

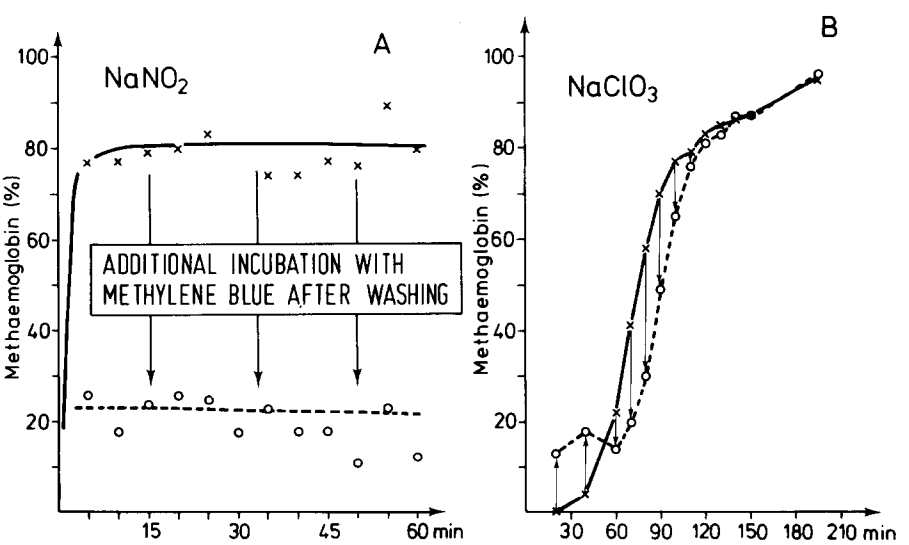

Fig. 3A and B. Methaemoglobin reduction with methylene blue. Washed erythrocytes were incubated at 37° C in NaCl-TRIS buffer (pH 7.4, NaCl 145 mM, TRIS 10 mM, Glucose 10 mM) with either sodium nitrite (10 mM; **A** ×−×) or sodium chlorate (30 mM; **B** ×−×). After the time indicated on the abscissa the erythrocytes were washed again and incubated in NaCl-TRIS buffer (without nitrite or chlorate) supplemented with 25 μM methylene blue for 3 h (O−O). Whereas methaemoglobin is nearly completely reduced after nitrite poisoning, the reduction by methylene blue is effective only in the early stages of chlorate poisoning

above 70%, the reaction becomes irreversible. There is good evidence that the same situation exists in vivo (Gordon and Brown 1947).

As a consequence of the pathophysiologic mechanisms, the preferred treatment in chlorate poisoning is an exchange transfusion before haemolysis and its complications occur. Gastric lavage is a standard procedure to eliminate the poison as well as haemodialysis or peritoneal dialysis. Sodium bicarbonate and heparin should be given, and methylene blue may be helpful in early stages of chlorate poisoning.

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