# Case reports

## Severe hydrogen sulphide poisoning treated with 4-dimethylaminophenol and hyperbaric oxygen

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**Key words**
Hyperbaric oxygenation, hyperbaric oxygen therapy, clinical toxicology, exogenous poison, resuscitation, outcome

**Abstract**
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**Introduction:** Hydrogen sulphide ($H_2S$) is a highly toxic gas which originates mainly during breakdown of organic matter under anaerobic conditions. After inhalation, $H_2S$ binds to mitochondrial respiratory enzymes preventing oxidative phosphorylation, thereby causing reversible inhibition of aerobic metabolism and cellular anoxia. The use of hyperbaric oxygen therapy (HBOT) for $H_2S$ poisoning remains controversial, but has a similar underlying rationale to that in carbon monoxide poisoning.

**Methods:** A retrospective review of patients with severe $H_2S$ intoxication who presented during 2006 and 2007 was carried out. Ten victims of severe occupational $H_2S$ poisoning were identified, of whom four died at the site of the accident. Two further patients required cardiopulmonary resuscitation at the site of the accident and the remaining four all received 100% oxygen followed by endotracheal intubation and artificial ventilation prior to hospital admission. In these six cases, 4-dimethylaminophenol was administered on admission as an antidote, followed immediately by HBOT using the schedule otherwise used in carbon monoxide intoxication.

**Clinical outcome:** The two patients who required cardiopulmonary resuscitation at the site of exposure died of cerebral ischaemia or pulmonary oedema on the first and seventh days after the accident respectively. The remaining four patients recovered without any neurological sequelae and were discharged for outpatient care after a median of nine days (range 8–12 days). No antidote-related adverse effects could be detected. Acid-base status and oxygenation improved and methaemoglobin fell with the first HBOT in all six cases.

**Conclusion:** In severe $H_2S$ intoxication, supportive HBOT may play a useful role in improving oxygenation and acid-base status quickly and counteracting the decrement in oxygen carriage caused by methaemoglobinaemia due to antidote administration.

### Introduction

Hydrogen sulphide ($H_2S$) is a colourless, flammable, highly toxic, irritant gas with a characteristic odour of 'rotten eggs'. This potentially life-threatening gas usually results from the breakdown of organic matter in the absence of oxygen and is released as a by-product of industry and agriculture. After inhalation, $H_2S$ is rapidly absorbed through the respiratory mucosa, distributing mainly into the lungs and brain. The mechanism of toxicity, with inhibition of oxidative phosphorylation, seems to be similar to that of cyanide and carbon monoxide (CO) poisoning.[1] The severity of clinical symptoms of $H_2S$ poisoning varies with the concentration and duration of exposure to $H_2S$; low concentrations cause respiratory tract irritation resulting in cough, dyspnoea and local mucosal soreness. With increasing concentrations of $H_2S$, neurological symptoms develop, high concentrations causing severe cerebral and pulmonary oedema which may lead to brain death, asphyxia and cardiopulmonary arrest (Table 1).[2]

The management of patients suffering from $H_2S$ intoxication remains a therapeutic challenge. The mainstay of treatment is rapid rescue from the site of exposure, immediate 100% oxygen, resuscitation as clinically indicated and administration of antidotes as early as possible. The use of hyperbaric oxygen therapy (HBOT) has been reported, but remains controversial.[3,4] We undertook a retrospective study of our experience at the Medical University Hospital, Graz, in managing acute severe $H_2S$ poisoning.

### Methods

We did a retrospective analysis of patients treated with HBOT in combination with 4-dimethylaminophenol therapy for severe $H_2S$ intoxication occurring in two industrial accidents in October 2006 and July 2007. The study was approved by the local ethics committee and was conducted in accordance with the precepts of the Declaration of Helsinki. Six out of 10 victims with severe intoxication (two males and four females, aged 26 to 60 years, mean 39.8 years) were

**Table 1**
**Health effects of hydrogen sulphide at various exposure levels**

| Concentration (ppm) | Effects |
|---|---|
| 2 | Chronic exposure: fatigue, headache, loss of appetite, weight loss, diarrhoea |
| 100 | Mild eye and lung irritation: 'gas eye', coughing, dyspnoea, sore throat |
| 200 | Olfactory paralysis |
| 300 | Pulmonary oedema, nausea, vomiting |
| 500 | Cerebral oedema, vertigo, dizzyness, somnolence, convulsions, loss of consciousness |
| 800 | Unconsciousness; death within 5 min |
| 1000 | Immediate collapse; asphyxia with cardiac arrest after inhalation of a single breath |

referred to our centre and are documented in this report. In fact, a total of 25 victims, of whom four died at the site, were involved in these two accidents. Twenty-one patients underwent HBOT at our department. Fifteen patients who suffered only mild intoxication are not included in this report. They were conscious and had no need of ventilatory assistance or circulatory support, but complained of mild symptoms such as headache, dizziness, nausea, emesis and dyspnoea, or had signs of mucosal irritation with cough, sore throat and/or eye strain ('gas eye'). The six severe cases who are the subject of this report had respiratory and circulatory shock, were unconscious and needed artificial ventilation and intensive circulatory support, including cardiopulmonary resuscitation in two patients.

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### PRE-HOSPITAL COURSE

The accidents occurred in large pelt-processing factories and tanneries during cleaning of or due to gas leakage from tanks containing rests of chromium sludge and sulphuric acid. In one case, an above-ground pipeline had leaked. None of the victims had worn protective equipment or clothing while working within endangered areas. Six workers collapsed immediately after taking a few breaths, fell unconscious and required cardiopulmonary resuscitation (CPR), performed by the local emergency doctors, after having been moved away from the site of $H_2S$ exposure by their co-workers. Two regained a circulation after 20 and 25 minutes of resuscitation respectively, but four died at the site of the accident. Four further victims were able to leave the site of exposure but then became unconscious immediately afterwards and developed acute respiratory failure and hypoxaemia, in three cases combined with arterial hypotension.

### INITIAL HOSPITAL MANAGEMENT

The six critically-ill, intubated and ventilated survivors were evacuated by helicopter to our centre. On admission, all remained comatose and in critical condition, with mid-dilated pupils and a Glasgow Coma Scale score of three. Mean systolic blood pressure was 13 kPa (range 11–15 kPa, 80–110 mmHg) and diastolic 8 kPa (range 4–9.3 kPa, 30–70 mmHg). Mean heart rate was 88 beats per minute (range 85–90 bpm). As first-line antidote, 3 mg per kg body weight of 4-dimethylaminophenol (4-DMAP) was administered intravenously. The time interval between accident and administration of 4-DMAP ranged from 60 to 90 minutes. In addition, 250 mg prednisolone was given intravenously. An emergency chest X-ray, electrocardiogram (ECG) and laboratory tests including carboxyhaemoglobin, methaemoglobin (MetHb), arterial blood gases and lactate were performed.

**Table 2**
**Biochemical and blood-gas measurements before and after the first HBOT**

| Patient | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| **Methaemoglobin (%)** | | | | | | |
| Pre-HBOT | 11.2 | 17.8 | 0.8 | 8.6 | 7.5 | 5.0 |
| Post-HBOT | 6.8 | 8.9 | 0.2 | 2.5 | 5.1 | 2.0 |
| **Lactate (mmol $L^{-1}$)** | | | | | | |
| Pre-HBOT | 4.3 | 2.0 | 1.3 | 2.9 | 1.3 | 12.4 |
| Post-HBOT | 3.5 | 1.5 | 0.5 | 1.7 | 1.3 | 8.4 |
| **$F_IO_2$ (%)** | | | | | | |
| Pre-HBOT | 100 | 100 | 100 | 100 | 100 | 100 |
| Post-HBOT | 100 | 40 | 50 | 70 | 90 | 40 |
| **$P_aO_2$ (mmHg)** | | | | | | |
| Pre-HBOT | 320 | 250 | 248 | 125 | 471 | 350 |
| Post-HBOT | 310 | 158 | 185 | 131 | 344 | 207 |

**Table 3**
**Patient characteristics and clinical course**
**(AF - atrial fibrillation; VF - ventricular fibrillation; ARDS - Adult respiratory distress syndrome)**

| Patient | Sex | Age (yrs) | CPR | Time to DMAP | Time to HBOT | Number HBOT | Diagnosis | Intubation (days) | ICU (days) | Hospital (days) | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 39 | Yes | 90 | 100 | 2 | VF, cerebral ischaemia & oedema pulmonary oedema, malignant hyperthermia | 1 | 1 | 1 | Death (day 2) |
| 2 | F | 40 | No | 60 | 100 | 6 | Respiratory shock, pleural effusions | 1 | 2 | 8 | Full recovery |
| 3 | F | 26 | No | 60 | 100 | 6 | Respiratory & circulatory shock, cerebral oedema | 1 | 2 | 8 | Full recovery |
| 4 | F | 46 | No | 60 | 100 | 11 | Respiratory & circulatory shock, pulmonary oedema, ARDS | 4 | 5 | 12 | Full recovery |
| 5 | M | 28 | No | 60 | 100 | 8 | Respiratory & circulatory shock, 'gas eye' | 1 | 2 | 8 | Full recovery |
| 6 | M | 60 | Yes | 90 | 125 | 1 | Cardio-respiratory arrest, AF, cerebral ischaemia & oedema pulmonary oedema, ARDS, artificial hypothermia | 7 | 7 | 7 | Death (day 8) |

HBOT

Bilateral myringotomies were performed, and the intubated, ventilated patients proceeded immediately to HBOT in the largest multiplace hyperbaric chamber in central Europe, which enables simultaneous treatment of up to five intensive care patients. HBOT was administered according to the protocol used in CO intoxication: first treatment; 304 kPa for 60 min then 223 kPa for 30 min; subsequent treatments were at 223 kPa for 90 min. Two HBOT were given within the first 24 hours, followed by a single daily HBOT until symptoms had subsided and the levels of MetHb were within the normal range. After HBOT, the patients were transferred to the intensive care unit for ongoing management.

The mean time interval between accident and the start of HBOT was 104 minutes (100–125 min). The median number of HBOT was 5.7 for all patients (range 1–11 treatments). HBOT was well tolerated. In these critically-ill patients, there was a short-term need for intensified circulatory assistance (enhancement of catecholamines intravenously), but after about ten minutes, all patients had stable cardiorespiratory parameters.

Arterial blood gas analysis was performed in every patient before and after the first HBOT (Table 2). The mean MetHb level fell by about 49%, from 8.5% to 4.3% (normal range 0.4–1.0% of total haemoglobin) and mean lactate decreased about 30%, from 4.0 mmol $L^{-1}$ to 2.8 mmol $L^{-1}$ (normal range 0.5–2.2 mmol L, whilst the mean pH increased slightly from 7.36 to 7.40. Furthermore, the inspired oxygen ($F_iO_2$) was lowered in five patients (mean post-HBOT $F_iO_2$ 65%). These data are summarised in Table 2.

CLINICAL COURSE AND OUTCOME

The two patients who required on-site CPR both had elevated cardiac biomarkers (myoglobin, creatine kinase-MB, lactate dehydrogenase and troponin T). The ECG in the other four patients revealed sinus rhythm without ST-elevation or any other signs of myocardial ischemia and no increase in cardiac biomarkers. Toxic lung oedema and adult respiratory distress syndrome were observed in three and two cases respectively, one of whom had required on-site CPR. Cerebral and thoracic CT-scans were performed to evaluate the severity of cerebral ischemia and cerebral or pulmonary oedema. Cerebral oedema and cerebral ischemia occurred in three patients, whilst one patient suffered from kerato-conjunctivitis and another victim developed small pleural effusions. One of the two CPR patients underwent artificial hypothermia (33$^{O}$C body temperature for 24 hours) after the first HBO treatment and received no further HBOT. The other post-resuscitation patient developed malignant hyperthermia (42$^{O}$C body temperature) after the second HBOT, and was given additional 4-DMAP, 3 mg per kg body weight. Other treatments comprised administration of mucolytic agents and bronchodilators, alone or in combination with corticosteroids. In all six patients, prophylactic antibiotic therapy was initiated in order to avoid pulmonary bacterial superinfection. The clinical courses of the six patients are summarised in Table 3.

## Discussion

Despite similarities to both cyanide and CO poisoning, the detailed pathogenic mechanisms of $H_2S$ poisoning are not fully understood.[5–7] Several antidotes, such as amyl or sodium nitrite and 4-DMAP, have been advocated.[2,8]

The main therapeutic goal of antidote administration is to inhibit sulphide binding to intracellular respiratory enzymes enabling sulphide detoxification and restoration of function of the oxidative chain. Both nitrites and 4-DMAP support the conversion of haemoglobin to methaemoglobin which readily binds to the toxic hydrosulphide anion until the latter is detoxified by haeme-catalyzed oxidation. Aerobic metabolism is enhanced by re-activation and protection of cytochrome oxidase. However, there is no clear evidence of their efficacy, and the emergency administration of antidotes that induce methaemoglobinaemia is not without risk.[2,8–10]

To be effective, nitrite therapy should be initiated within the first few minutes after $H_2S$ poisoning.[2,8] It is postulated that nitrite-induced methaemoglobinaemia occurs preferentially under poor oxygen conditions.[11] An oxygen-enriched environment, such as during resuscitation and/or ventilation with oxygen, may favour sulphide depletion, and nitrite administration may actually slow sulphide removal under these circumstances. Other adverse effects of nitrites are hypotension, tachycardia, vomiting, headache and biochemical interaction with haemoglobin-oxygen dissociation due to excessive nitrite-induced methaemoglobinaemia. In contrast to most other reports, we used DMAP as the initial antidote, and adverse effects of methaemoglobinaemia were not observed.

Isolated case reports have suggested that HBOT may be effective in the treatment of excessive methaemoglobinaemia.[8,12–15] The biochemical mechanism for this is based on enhanced reduction of methaemoglobin levels due to prevention of the oxidation of haemoglobin. In our series, considerable methaemoglobinaemia was caused by inhalation of high concentrations of $H_2S$ and not due to administration of the antidote 4-DMAP, which caused no apparent side effects in our patients.

Further useful effects of HBOT are increased tissue oxygen tension, vasoconstriction, reduction in cerebral oedema, a decrease in leucocyte adhesion, down-regulation of inflammatory mediators and enhancement of nerve cell regeneration.[16–19] HBOT at 304 kPa has been shown in an animal model to be effective in treating $H_2S$ poisoning, particularly in combination with early sodium nitrite therapy.[20] Case reports in human victims also appear promising.[2,8,12,21–23] Neurological symptoms appear to respond readily to HBOT, and neurological sequelae may be prevented, even if HBOT is delayed.[21–26] These reports and our own experience would suggest that the role of HBOT in severe $H_2S$ poisoning is probably supportive rather than as an antidote.[8,12] In addition, in cases of antidote-related side effects, e.g., respiratory insufficiency, or failure of antidote therapy, HBOT may be the treatment of choice. Moreover, the extent of concomitant cerebral and/or pulmonary oedema, which is often observed in severe cases, can be decreased significantly by HBOT, possibly resulting in reduction of the mortality rate.[22] Objective benefits from HBOT in the present patient series were the reduction in MetHb and an improvement in acid-base status and oxygenation, as documented with the first therapy. Despite this, the mortality in severe $H_2S$ intoxication remains high.

Despite successful use in both experimental and clinical $H_2S$ intoxication, an optimal dose or duration of HBOT has not been established.[2,8,12,21–23] Given the somewhat similar pathogenic mechanisms to CO intoxication, it would seem justified to treat $H_2S$ intoxication using regimens similar to those described for CO poisoning.[27]

## Conclusions

Supportive HBOT in severe $H_2S$ intoxication ensures rapid correction of hypoxia and counteracts any antidote-induced decrement in oxygen transport capacity caused by MetHb. HBOT not only enables and/or supports efficient emergency treatment but appears to help avoid neurological sequelae. Even when first-line antidote therapy has failed and/or side effects have occurred, a benefit from secondary HBOT can be achieved. Controlled clinical studies of HBOT for $H_2S$ poisoning are needed, but will be difficult to achieve given its rarity and the limited access to hyperbaric facilities.[28] In the meantime, cases series such as this are the best evidence available.

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