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Outcome after hydrogen sulphide intoxication☆

Eline A.Q. Mooyaart[a], Egbert L.G. Gelderman[a], Maarten W. Nijsten[b], Ronald de Vos[a,c], J. Manfred Hirner[a,c], Dylan W. de Lange[d], Henri D.G. Leuvenink[e], Walter M. van den Bergh[b,*]

[a] Department of Anesthesiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[b] Department of Critical Care, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[c] Mobile Medical Team, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[d] Department of Intensive Care Medicine and National Poison Information Center (NPIC), University Medical Center Utrecht, University of Utrecht, Utrecht, The Netherlands
[e] Surgical Research Laboratory, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

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ABSTRACT

Aim: Hydrogen sulphide (H_2S) intoxication in man is frequently associated with a fatal outcome. In small animal models hydrogen sulphide has demonstrated profound protection against hypoxia. No reports that focus on a potential protective effect in humans have been published.
Methods: The frequency and outcome of a large cohort of hydrogen sulphide intoxications is described.
Results: From 1980 until 2013, 35 accidents totalling 56 victims occurred of whom at least 24 (43%) survived. Of the 8 patients with documented cardiopulmonary resuscitation on the scene, 6 (75%) survived. In some of these cases with good outcome the exposure time to very high hydrogen sulphide levels before extraction and resuscitation was more than 45 min.
Conclusion: Manure related hydrogen sulphide intoxication is associated with a high mortality, although in some cases, recovery appears to be far more favourable than the initial presentation would suggest. Possibly protection from hypoxic injury due to induction of a suspended animation-like state by hydrogen sulphide may be responsible.

Introduction

When Heracles was assigned to clean the Augean stables he managed the job by rerouting two rivers through the stables that flushed out the cow dung. This was of course a wise thing to do as it saved him considerable work, and in addition prevented him from inhaling manure gas. Today's manure storage tanks have to be cleaned more often than once in every 30 years as was the case in King Augeas' stables, but the concentration of manure gas emanating from the stored manure can be very high. One of several gases produced by decomposition of biological material is the neurotoxin hydrogen sulphide, which in small amounts is detectable by its foul smell. Hydrogen sulphide (H_2S) is a highly toxic gas that can be rapidly fatal for workers that are exposed in installations such as manure tanks that release this compound. Many case reports and cohort studies bear witness to the lethal effects of exposure to hydrogen sulphide with often multiple fatalities.[1]

However, we recently observed that a cohort of patients admitted to the ICU after out-of-hospital cardiac arrest due to an evidently very high exposure to hydrogen sulphide displayed survival that was better than expected. Furthermore, recent animal research has demonstrated that hydrogen sulphide confers strong protection against ischemia and reperfusion injury. We therefore hypothesised that in humans, apart from its toxic effect, hydrogen sulphide may also have potential protective effects that attenuates post-anoxic encephalopathy after cardiac arrest.

The aim of our study was to clarify the incidence and outcome of hydrogen sulphide intoxications with an emphasis on outcome after cardiopulmonary resuscitation and ICU admission. For that purpose we summarize the outcome of all hydrogen sulphide intoxications in the Netherlands from 1980 until 2013 and review the literature on the mechanisms of action, both toxic and protective, of hydrogen sulphide.

☆ A Spanish translated version of the summary of this article appears as Appendix in the final online version at http://dx.doi.org/10.1016/j.resuscitation.2016.03.012.

* Corresponding author. Fax: +31 050 3615644.
E-mail address: w.m.van.den.bergh@umcg.nl (W.M. van den Bergh).

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Methods

After an accident with a manure store tank in which three out of four victims died the Dutch Safety Board performed a comprehensive investigation on the incidence and outcome of all consecutive suspected hydrogen sulphide poisonings in the period 1980–2013 in The Netherlands.[2] There was no existing overview of all manure related accidents so the Dutch Safety Board made an inventory with the use of: (1) the databank of Mrs. J. Middelkoop, Advisor Hazardous Substances of the Fire brigade Amsterdam-Amstelland and expert on the hazards of manure gasses; (2) Stigas, a knowledge institute that advices employers and employees in the agricultural sector on safety issues and healthy work environment; and (3) the Inspectorate SZW (Social Affairs and Employment) whose investigational task includes the supervision of compliance with the regulations in the area of working conditions and the prevention of major hazards involving dangerous substances. The acquired information was completed with information from the internet. For background information interviews had been performed with employees of the Dutch Federation of Agriculture and Horticulture (LTO Nederland), the branch organisation for enterprisers in agriculture (CUMELA), and the union of Dutch milk cattle breeders (NMZ).

We examined the results of this public report in detail and identified patients who had cardiopulmonary resuscitation at the scene to compare the outcome of these patients with out-of-hospital cardiac arrest in general.

For the detailed description of a patient who was admitted to our hospital we obtained oral and written informed consent according to the requirements of our Medical Ethical Committee.

A review of the literature is provided to clarify the postulated mechanism of neuroprotection by hydrogen sulphide.

Results

From 1980 through 2013 there were 35 accidents in the Netherlands with manure storage involving 56 adults with hydrogen sulphide intoxication (Table 1). Of these 56 patients 24 are known to have survived, indicating a 43% survival rate (Table 2), but 3 others most probably also survived as they were discharged alive from the ICU, which would raise the survival rate to 48%. Most fatal endings tragically happened to the ones that came to the rescue of others in jeopardy and many times there was more than one casualty. Remarkably, several fatalities involved victims who entered the toxic environment last and several survivors were those who had the longest exposure time (Table 2).

When all 8 patients during the period from 1980 through 2013 who had documented cardiopulmonary resuscitation on the scene are considered, 6 (75%) survived without neurological complications (Table 2).

There were 4 events of hydrogen sulphide intoxication within the last five years with a total of 10 adult patients of which 6 were declared dead at the scene and four who were admitted to an ICU.

In one event the single victim was declared death at the scene.

In a second event, involving both father and son, the son died while the father recovered after being admitted at the ICU. They were cleaning a barn, while at the same time manure was mixed with water in order to create a solution that would be easier to spread out on the farmland. Both were found unresponsive by a trespassing person, who alerted the emergency services. It was not clear how long they had been unconscious. Resuscitation was initiated, however, without success for the son who was declared dead on the scene.

The third event involved three non-related victims in which two victims made a good recovery and one died. One was cleaning an empty truck tank normally carrying manure. He became unresponsive, after which his colleague entered the tank to help. When he too did not answer, a third person climbed into the tank, while a fourth called the emergency services. After fifteen minutes, all three were extracted. Resuscitation resulted in return of spontaneous circulation (ROSC) in all three, though their Glasgow Coma Score remained 3. They were admitted to the ICU. Two regained consciousness and could be extubated the next day. The third person, who had entered the tank last, never woke up and eventually died.

The fourth event involved four non-related victims in whom one made a good recovery and while the three others died. An employee of a professional cleaning company became unresponsive while cleaning the bottom of a manure tank, although he wore an oxygen mask. His colleague climbed down the tank for assistance and collapsed as well. A wage labourer as well as the farmer's son noticed something was wrong and both entered the tank without oxygen in order to try and rescue the other two. The farmer had discovered the disaster at the manure tank and alerted the emergency services. Pending the arrival of the paramedics the farmer, who knew that his son was inside, unsuccessfully attempted to open the tank with a forklift truck. After a 45-min rescue operation the four victims were extracted. The two professional cleaners and the farmer's son were pronounced dead at the scene after fruitless resuscitation attempts were made. The 23-year old wage labourer (patient 55, Table 1) had no cardiac action after he was extracted, but after some chest compressions and ventilation, he quickly restored to normal sinus rhythm with ROSC. He showed some movement of his limbs, but had no sign of spontaneous breathing and therefore was intubated at the scene. Thirty minutes after the start of resuscitation, this patient arrived at our University Hospital where he was admitted at the ICU. The patient was sedated with propofol and treated with controlled hypothermia with a target temperature of 33 °C for 24 h after which he was passively warmed to 36 °C in approximately 3 h after which sedation was stopped. After 12 h without sedation his neurologic examination revealed no signs of improvement. No additional examinations like an electric encephalogram (EEG) or somatosensory evoked potential (SSEP) were ordered. Ninety-six hours after his extraction from the tank, the first progression in his consciousness was seen with a motor score that fluctuated between M2 and M4. During the following week his neurological state steadily improved to E4M6V1. At that time, nine days after the accident, he was discharged to the ward where further neurologic evaluation took place. He showed involuntary movements and although he had a clear consciousness and nodded correctly if he was asked a simple question, he appeared to be mute. Furthermore, he displayed a slight left-sided hemiparesis.

Twenty-three days after the event he was transferred from the hospital to a rehabilitation centre. His GCS at that time remained E4M6V1. After 4 months, he came in walking without support to visit our ICU and spoke, although still bradyphrenic and with a dysarthric speech and restricted vocabulary. His hemiparesis had disappeared. Furthermore, his mother informed us that he could already drive the tractor again.

In summary, four out of five (80%) patients who were admitted to an ICU in the last 5 years after hydrogen sulphide intoxication made a good recovery.

Discussion

Hydrogen sulphide intoxication in manure barns is evidently a very severe event since it was associated with more than 50% mortality. It underscores the danger of working with large quantities of manure in restricted spaces. However, the survival rate of the 8 patients with documented CPR (75%) after hydrogen sulphide intoxication is far better compared to survival rates of OHCA

Table 1
Overview of the 56 victims involved in the 35 accidents between 1980 and 2013.

Event	Victim	Age	Sex	Year	Location Incident	Outcome at farm	Follow-up
1	1	27	M	1980	Manure basement	DOSc	
	2	58	M	1980	Manure basement	DOSc	
2	3	Adult	M	1981	Manure basement	Loss of consciousness	Unknown
	4	60	F	1981	Manure basement	DOSc	
	5	Adult	M	1981	Manure basement	Loss of consciousness	Unknown
3	6	32	M	1982	Manure basement	DOSc	
	7	59	M	1982	Manure basement	DOSc	
4	8	45	M	1984	Manure basement	DOSc	
5	9	40	M	1984	Manure basement	DOSc	
	10	44	M	1984	Manure basement	DOSc	
6	11	Adult	M	1989	Manure tank	DOSc	
	12	Adult	M	1989	Manure tank	DOSc	
7	13	Adult	M	1990	Manure basement	Loss of consciousness	Survived
	14	Adult	M	1990	Manure basement	Loss of consciousness	Died 2 weeks later
8	15	6	M	1990	Barn with manure mixer	DOSc; unsuccessful resuscitation	
9	16	Adult	M	1991	Manure tank	DOSc; unsuccessful resuscitation	
10	17	Adult	M	1992	Manure basement	Loss of consciousness	Survived
	18	Adult	M	1992	Manure basement	Loss of consciousness	Survived
	19	Unknown	M	1992	Manure basement	DOSc	
11	20	Adult	M	1996	Manure tank	DOSc	
12	21	Adult	M	1998	Manure basement	DOSc	
13	22	Adult	M	1999	Manure basement	DOSc	
14	23	Adult	M	2000	Manure tank	Loss of consciousness	Survived; no permanent damage
	24	Adult	M	2000	Manure tank	Critical	Survived; no permanent damage
	25	23	M	2000	Manure tank	Critical	Survived; no permanent damage
15	26	Adult	M	2001	Manure on field by accident	Loss of consciousness	Unknown
16	27	37	M	2003	Manure basement	DOSc	
17	28	Adult	M	2003	Manure basement	No complete loss of consciousness	Survived
18	29	Adult	M	2004	Barn with manure mixer	DOSc	
19	30	61	M	2008	Barn with manure mixer	DOSc	
	31	33	M	2008	Barn with manure mixer	DOSc	
20	32	Adult	F	2008	Barn with manure mixer	No complete loss of consciousness	Survived
21	33	5	M	2009	Barn with manure mixer	Successful resuscitation	Survived
22	34	23	M	2009	Manure tank	Loss of consciousness	Died
	35	Adult	M	2009	Manure tank	Loss of consciousness	Survived
23	36	Adult	M	2009	Manure mixer	Intubated	Extubated after 7 days; permanent neurologic damage
24	37	25	M	2009	Manure tank truck	Successful resuscitation	Extubated next day; DC 8 days; no permanent damage
	38	20	M	2009	Manure tank truck	Successful resuscitation	Extubated next day; DC 4 days; no permanent damage
	39	Adult	M	2009	Manure tank truck	Successful resuscitation	Died
25	40	Adult	M	2010	Manure tank	DOSc	
26	41	2	F	2010	Manure drainage pipe	Loss of consciousness	Survived; no permanent damage
27	42	11	M	2010	Barn with manure mixer	Successful resuscitation	Survived; no permanent damage
28	43	Adult	M	2010	Barn with manure mixer	Loss of consciousness	Pulmonary edema; survived
29	44	Child	M	2010	Barn with manure mixer	Loss of consciousness	Pulmonary edema; survived
30	45	Adult	M	2010	Barn	No complete loss of consciousness	DC 1 day
	46	Adult	M	2010	Barn	No complete loss of consciousness	DC 1 day
	47	Adult	M	2010	Barn	No complete loss of consciousness	DC 1 day
	48	Adult	M	2010	Barn	No complete loss of consciousness	DC 1 day
31	49	Adult	M	2011	Fall into manure tank	DOSc; possibly due to trauma	
32	50	Child	M	2013	Barn with manure mixer	Loss of consciousness	Survived
33	51	4	M	2013	Manure well	Critical	Unknown
34	52	Adult	M	2013	Manure tank	DOSc	
	53	Adult	M	2013	Manure tank	DOSc	
	54	Adult	M	2013	Manure tank	DOSc	
	55	23	M	2013	Manure tank	Successful resuscitation	Extubated 9 days later; DC 14 days; resumed work after 4 months
35	56	Adult	M	2013	Barn with manure mixer	No complete loss of consciousness	Survived

Victims are in chronological order. In case of multiple victims, the first mentioned is the first that probably came in contact with hydrogen sulphide. M: male; F: female; DOSc: dead on scene; ROSC: return of spontaneous circulation; DC: discharge from hospital

(5–8%) in general. Furthermore, survival after admission to an ICU (80%) was also better than survival of patients admitted to an ICU alive after OHCA (approximately 50%), although these cohorts are not really comparable.[3]

This relatively good outcome may be explained by the fairly young age and presumably good health of most victims, but also by the protection from hypoxic injury by the induction of a suspended animation-like state by hydrogen sulphide. The aetiology of the event, asphyxia, is probably not a good explanation for better outcome as outcome after asphyxia is often worse. The remarkable recovery of patient nr. 55 (Table 1) after prolonged exposure to evidently extremely high hydrogen sulphide levels suggest that protection to hypoxic injury might be conferred.

Several limitations of our study have to be addressed. First, in the described cases, no further information on the composition of the inhaled gasses was available. Only in event 27 hydrogen sulphide measurements were taken at the scene and a concentration of 934 ppm was found. It is plausible that other gasses that develop during the protein rotting process may have been of influence to the nature of the accidents described. Blood concentration

Table 2
Characteristics of victims and their outcome.

Demographics	*N* (%)
Number	56
Mean ± SD age[a]	30 ± 19
Male	53 (95%)
Adult	49 (88%)
Dead on scene	25 (45%)
Cardiopulmonary resuscitation on scene	8 (14%)
Survived without neurologic complications	*6 (75%)*
Admitted to hospital[b]	28 (50%)
Admission to ICU[c]	15 (27%)
In hospital mortality[d]	3 (11%)
Overall survival[e]	24 (43%)

[a] Exact age unknown in 21 cases.
[b] Admission to hospital unknown in 3 cases.
[c] Admission to ICU unknown in 8 cases.
[d] In hospital mortality unknown in 4 cases.
[e] Overall survival unknown in 4 cases (of which 3 most probably survived as they were discharged alive from the ICU, which would increase survival to 48%).

Table 3
Reported effects of hydrogen sulphide (H_2S) in humans.

Concentration ppm	Effect
0.02–0.03	Smell is detectable
1.5	Maximal allowed concentration when exposed daily for 8 h
5–10	Unpleasant penetrating smell
>50	Ocular conjunctiva irritation
100–200	Olfactory nerve paralysis (i.e. loss of the scent); upper respiratory tract irritation
250–500	Excitement, headache, cyanosis, pulmonary edema
500–700	Ataxia, nausea, dizziness, unconsciousness, respiratory paralysis; lethal after 30 min
>1000	nervous system paralysis, diaphragm paralysis after one breath; death within minutes
>5000	Imminent death

ppm: parts per million; 1 ppm of hydrogen sulphide (molecular weight 34) equals 1.4 mg hydrogen sulphide per m^3. *Of note*: Humans are exquisitely sensitive to the smell of hydrogen sulphide. Loss of ability to smell hydrogen sulphide due to olfactory nerve paralysis is an early manifestation of intoxication.

measurements of hydrogen sulphide or other toxic fumes that appear when protein decomposes were not taken in any case. Although hydrogen sulphide levels in air can be accurately measured with widely available equipment, it is notoriously difficult to measure and to quantify hydrogen sulphide in tissues. This is related with the complex interaction of hydrogen sulphide with proteins. Besides the fact that hydrogen sulphide is not easily measured in blood, it is currently not clear what the implications are when an elevated hydrogen sulphide concentration becomes evident.[4]

Second, the cause of death in victims that died during their hospital admission is not known for all cases. Besides the extremely bad neurological outcome due to suffocation, other causes of death such as respiratory failure due to manure inhalation or ARDS are to be considered.

Third, in many cases the fire brigade had to be alarmed in order to extract the victim or victims. Although time of exposure could only be retrieved in cases 24 and 34, it can be assumed that most victims had at least an exposure time of longer than 7 min and 53 s, which is the average time for the fire brigade to arrive at the scene after being alarmed in the Netherlands. When taking into account the time it may take to notice there is a manure gas related problem, make an alarm call, wait for emergency services to arrive, and the time it takes for them to make a plan for extraction and gear up, the exposure time could easily exceed 15 min.

Toxic effects of hydrogen sulphide

Hydrogen sulphide is one of several gases produced by decomposition of biological material. Hydrogen sulphide has for long been appreciated for its toxicity. It was used in 1916 as a poison gas during World War I by the British army.[5] Not only has hydrogen sulphide deleterious effects, it is highly explosive when mixed with air. Its foul smell of rotten eggs can be detected at a level as low as 0.02 ppm (Table 3). Up to 100 ppm, it mainly causes mucosal irritation, such as eyes, nose and throat prickling, coughing, sneezing and tear production. Then, at a dosage up to 1000 ppm, the physiological effects become more serious. A treacherous property of hydrogen sulphide is that paralysis of the olfactory nerve occurs, making the detection of hydrogen sulphide through nasal warning impossible. Furthermore, neurological, pulmonary and cardiac symptoms like ataxia, dyspnoea and arrhythmia will develop. At a dose higher than 1000 ppm, collapse with respiratory paralysis typically occurs within minutes, leaving the victim surrounded by even higher concentrations, since hydrogen sulphide is heavier than air and therefore tends to accumulate in lower parts of a compartment.[6]

Hydrogen sulphide inhibits cytochrome oxidase, which is an important mitochondrial enzyme in the mitochondrial electron transport chain and is involved in the reduction of oxygen to water.[7,8] The mitochondrial electron transport chain comprises a very complex system of proteins that is coupled with the citric acid cycle to produce adenosinetriphosphate (ATP). Upon binding to cytochrome oxydase hydrogen sulphide prevents cytochrome oxydase to combine electrons with oxygen and thus prevents the reduction of oxygen to water, creating chemical suffocation and preventing ATP formation.[8,9]

Protective effects of hydrogen sulphide

Recently it was discovered that hydrogen sulphide has not only toxic effects.[10] When exposed to hydrogen sulphide mice can enter a state of suspended animation from which they could be aroused by stopping the exposure to hydrogen sulphide and supplying extra oxygen. The mice appeared to be healthy and apparently fully recovered from their hydrogen sulphide -induced coma. Animal studies have shown that mice breathing a combination of hydrogen sulphide and oxygen gradually went into hibernation, decreasing their metabolic rates by slowing both heart rate and breathing frequency and reducing body temperature.[10,11] In another experiment it was shown that hydrogen sulphide might even protect against hypoxia. Mice were exposed to hydrogen sulphide and an air mixture with only 3% oxygen.[12] The mice survived for 6.5 h and when the hydrogen sulphide was stopped and the oxygen levels were increased to normal, the mice went back to normal as well. They appeared to have entered a state of suspended animation that could be reversed by administering oxygen instead of hydrogen sulphide. When repeating experiments in larger mammals, however, these results could not be reproduced and toxicity of hydrogen sulphide appeared to be a more dominant feature, which may be related to challenges in administering inhaled hydrogen sulphide in larger animal sizes.[13,14]

Since the discovery that hydrogen sulphide could induce suspended animation, new discoveries have been made. It has long been known that hydrogen sulphide is formed when sulphur-containing organic material e.g. proteins deteriorates. However, it became apparent that hydrogen sulphide is endogenously produced in small amounts as well and that it plays a role as a secondary messenger in cellular signalling. Hydrogen sulphide is considered a gasotransmitter, a signalling gas, forming a threesome with carbon monoxide (CO) and nitrogen oxide (NO), sharing some

of the properties of CO and NO. Like NO, hydrogen sulphide causes smooth muscle relaxation, underscored by studies in cystathionine γ-lyase knockout mice that showed these mice had a higher mean blood pressure when exposed to hydrogen sulphide as compared to wild-type mice.[15] It is thought that hydrogen sulphide promotes angiogenesis, smooth muscle relaxation, anti-inflammation, radical oxygen scavenger, coagulation and many more.[16] The potential protective properties against hypoxia were explored in a series of experiments in which livers or kidneys were subjected to severe ischemia. Exposure to hydrogen sulphide before ischemia almost completely blocked ischemic injury even without the protective effect of hypothermia.[9,17] Hydrogen sulphide also protects against lung injury in a rodent model of ventilator induced lung injury and reduces organ dysfunction in a pneumosepsis model.[18] Furthermore in a rodent model hydrogen sulphide shows neuroprotection in traumatic brain injury.[19] This is likely due to the induction of a suspended animation-like state by hydrogen sulphide.

Clinical implication

Our observations may have several clinical implications. The aetiology of cardiac arrest is thought to be asphyxia due to very low oxygen concentrations and large amounts of hydrogen sulphide. However, the outcome is far better than in patients in whom asphyxia is the cause of cardiac arrest.[20] It is plausible that the neuroprotective ability of hydrogen sulphide is the reason for the difference in outcome. Therefore, we argue that CPR should be performed for a prolonged time when hydrogen sulphide is suspected or considered a possible cause for the cardiac arrest.

Extraction of the victim may be very dangerous as attested by the clustering of 53 patients in 35 accidents. Thus emergency teams have to be prepared for more victims than may be anticipated. Furthermore, due to its relative density of 1.2 (air = 1), hydrogen sulphide accumulate in the lower part of the tank. Safety regulations therefore require that cleaning has to be done by two persons: one has to descend, carrying an oxygen tank to prevent hydrogen sulphide inhalation, the other stays above to assist or call for help when required.

Humans are able to detect hydrogen sulphide below the detection threshold of 5 ppm of that for example is achieved by the portable hydrogen sulphide measuring device that is used by the our fire brigade (GasAlert Extreme, BW Technologies by Honeywell, Calgary, Canada). It seems therefore reasonable as well as prudent to perform the following on-the-scene analyses if an intubated patient is suspected of hydrogen sulphide intoxication. First connect a hydrogen sulphide detector to the expiratory part of the breathing circuit. Only if the detector measures no hydrogen sulphide, the range may be lower than 5 ppm and directly smelling the expired air can be attempted. Portable quantitative hydrogen sulphide detectors are easily available and sometimes integrated into portable detection systems for carbon monoxide levels that are used by fire brigades. It has even been demonstrated that hydrogen sulphide levels can be measured from victims. If portable detection equipment is not available, we advise to obtain a 10 ml syringe sample of expired air to be used for analysis at a later stage.

Scientific implications

If indeed protection by hydrogen sulphide plays a role in the relatively good outcome of our cohort study, a first and most pressing question is why the very promising results of hydrogen sulphide in small animals such as mice have not been reproduced in larger animals. One rather theoretical explanation may be that the with larger body sizes, the "pharmacokinetics" and "pharmacodynamics" change in such a manner that hydrogen sulphide protection and intoxication will overlap too much.

Conclusion

Although by far the largest cohort of patients with hydrogen sulphide intoxication, conclusions are limited by ultimately small numbers of patients suitable for comparison with patients after OHCA or ICU admission. However, larger patient data are unlikely to become available in the near future and the outcome of this cohort is in striking contrast with data from previous, very small, cohorts in which outcome was almost always fatal. This and the delayed recuperation displayed by some of the patients may have the consequence that scepticism about prognosis may be unjustified and that commonly used clinical decision trees for prediction of prognosis are not appropriate for this group of patients.[3,21]

Although stated with great reluctance the conclusion of this study is that case fatality rate after cardiopulmonary resuscitation due to severe hydrogen sulphide intoxication may be relatively good when compared to OHCA in general. Protection from hypoxia and ischemia by hydrogen sulphide through induced hibernation may play a role.

Conflict of interest statement

All authors declare that they have no conflict of interest.

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None.

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