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Exposure to hydrogen peroxide – under the toxicologist eye

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Abstract

Introduction: Hydrogen peroxide is well soluble, odourless and colourless liquid with syrup consistency. It has different application depending on concentration. In 3% of concentration is present in almost every home as a disinfectant product, in higher concentration (35%) is used in pharmaceutical, chemical and cosmetic industry.

The aim of the study: The purpose of this systemic review was to collect and analyse causes and possibilities of treatment a patient after ingestion a caustic substance.

Material and method: Standard criteria were used to review the literature data. The search of articles in the PubMed and Google Scholar database was carried out using the following keywords: hydrogen peroxide, exposure, toxicology.

Description of the state of knowledge: Exposure for hydrogen peroxide is not very common and most of the times is unintentional, except suicide attempts. Because it is a caustic substance and the main route of exposure is ingestion, most of symptoms are due to damage

of gastrointestinal tract. However, the consequences of exposure range from short-time illness to brain damage or even death.
Summary: Patient after exposure to >30% hydrogen peroxide should receive a complex treatment. Physicians need to be alert to the symptoms of not only gastrointestinal tract but also CNS. The patient may require specialized care by many specialists.

Key words: hydrogen peroxide, exposure, toxicology

Introduction

Caustic substances are well accessible, can be found in almost every home in the form of household cleaners, hair oxidizer and drain cleaners. Despite the potential danger, people still tend to keep those substances unsecured and in the unlabeled containers. This can lead to unintentional exposure to caustic substances, very often affecting children. Caustic substances are associated only with acids and basis, but it is not the end of that list. Oxidants, detergents, potassium salts, zinc salts and phenols also belong to that group.

Caustic substances cause direct tissue damage [1]. In case of acids there is a tissue dehydration, mainly proteins, which leads to coagulation necrosis. This process results in stable tissue formation that may be able to protect deeper layers of the gastrointestinal wall from further penetration of acids and as a consequence developing complication [2]. The exception is hydrofluoric acid which causes colliquative necrosis. Acids usually tends to have specific taste and smell. Usually we observe stomach damage and most often esophagus is saved. Vomiting as a defensive reflex is preserved and protects from swallowing. The other protecting factor is pyloric contraction that prevents further acid penetration [2].Bases are odourless and tasteless substances, they are swallowed before defensive reflexes such as vomiting, gastric cardia and pylorus spasm are started. Half of this type of cases occur with damage of esophagus, mostly affects upper 2/3 of esophagus and often burns of small intestine. In case of exposure to bases we observe colliquative necrosis. During this process heat and gases are released and they are additional damaging factor. Ingestion of bases is more dangerous than acids [2]. In this case inflammation is significantly stronger and also another factor is that it comes to bacterial colonization of the gastrointestinal tract. In the result, we observe fibrosis and stricture formation which are stronger and more dangerous than in case of acid ingestion. Comparing acids and bases, first ones cause less intense edema-inflammatory changes and less fibrosis and stricture formation.Despite that acid ingestion is less dangerous than base, both can lead to heave damage of wall of gastrointestinal tract with the formation of ulcers, intense bleeding and perforation with multi-organ damage. Degree of damage depends mainly on pH. It is recognised that strong acid is substance with $pH < 2$ and strong base $pH > 12$. We can also measure the strength of caustic substance by titratable acid/ alkali reserve (TAR). TAR determines the volume of neutralizing agent needed to restore pH of consumed substance to pH which is physiologically present in our gastrointestinal tract [2].

Hydrogen peroxide is an inorganic compound from the peroxide group with the formula H_2O_2. It has strong oxidizing properties because of the effect of creating atomic oxygen during its decomposition. In most cases the only effect of intoxication is burn of gastrointestinal tract [1]. In case of ingestion caustic substance in patient's history the most important is to identify if there are symptoms of damage to the mucous membrane of the upper gastrointestinal tract and respiratory tract. It is highly important to mind on alarm symptoms of those damages such as dysphagia, heamatoptysis, fever (all of alarm symptoms

are shown in a table S1) [2]. Hydrogen peroxide is caustic substance, it is especially dangerous in higher concentrations >30%. Because of that it usually causes burn of gastrointestinal track, very rarely it can cause symptoms from central nervous system. Therefore people after ingestion caustic liquid are more surgical patients than toxicological. Despite this, they are usually hospitalized in the Toxicology Department. Caustic substance ingestion is commonly unintentional and mostly found in children [3,4]. There is few statistical data, but in one study of more than 95000 intoxications, 0.34% were caused by hydrogen peroxide, of those 60% occurred in children and 85% occurred by ingestion [5].

Dealing with patients after ingestion of caustic substance is similar for every type of substance. There are several rules which need to be followed to improve the prognosis and reduce complications. There are several information that doctor can receive from the history of a patient exposured to caustic substances that can indicate significant damage of gastrointestinal track. These are: poisoning for purpose of suicide, a long time of contact of the substance with mucosa membrane, a liquid form of a substance, intake of the substance on an empty stomach, vomiting in a short period of time from consumption or if the patient had vagotomy or resection surgery. [2]

It is commonly known that caustic substances cause local damage to gastrointestinal track. However, it is not that common to know that they can also be a reason of systematic actions, such as: metabolic acidosis, shock, hemolysis, spreading necrosis of tissues with increased production of lactic acid or even venous or arterial gas embolism in central nervous system (CNS) or in portal vein [2]. Hydrogen peroxide is one of these dangerous caustic substances.

Table 1. Alarm symptoms.

Alarm symptoms	
Increased salivation	Irritation of mucous membrane of oral cavity
Dysphagia	Odynophagia
Aphonia	Stridor
Cough	Hoarseness
Suffocation	Spontaneous vomiting
Thorax and abdomen pain	Fever
Tachycardia	Haematoptysis

Pathophysiology

Hydrogen peroxide causes toxicity via three main mechanisms: corrosive damage, oxygen gas formation and lipid peroxidation[6]. Exposition on 3-5% hydron peroxide irritates mucous membranes and eyes if there was an ocular exposure, lacrimation and blurred vision will appear. A little higher concentration (10%) will lead to inflammation and blistering during dermal contact and ulceration of cornea in ocular exposure [6,7]. The main effect of ingesting hydrogen peroxide is irritation of gastrointestinal tract which results as a foaming at the mouth, nause, vomiting and haematemesis. Foam may be the reason of respiratory track obstruction or pulmonary aspiration. There are three stages of upper gastrointestinal tract damage that are shown in table 2 [2].

Table 2.

Stage	Duration	Description
Acute damage phase	4-7 days	This stage is followed by necrosis, thrombosis and demarcation necrosis tissues. Necrosis and thrombosis reach the maximum in first 24-48 hours. Demarcation with creating of ulcers occurs between 3-4 days after ingestion.
Late phase of granulation	8-14 day	Inflammatory infiltration and granulation tissue begins to fill the damage area around half of first week since ingestion. In the same time fibroblasts activity appears. In the end of the first week collagen replaces granulation tissue. Gastrointestinal tract perforation is most likely in this stage.
Phase of chronic scarring	2-4 week	We observe creating of fibrous connective tissue with formation of stricture.

One millilitres of 3% hydron peroxide can release ten millilitres of oxygen while one hundred millilitres of 35% solution can release about 12-14 liters of oxygen gas on contact with organic tissue in the presence of catalase [7]. As a consequence of liberation of large volumes of oxygen in the stomach, painful gastric distension and belching may occur. Chemical colitis is another complication. This inflammation of the large intestine is thought to be secondary to the chemical reaction resulting in penetration of highly reactive oxygen species, resulting in damage to the colonic mucosa [8,9]. Hydrogen peroxide enteritis with 3% solution can cause instant bubbling on the mucosal surface followed by a whitening of the mucosa termed the 'snow white' sign [10,11]. Extreme amounts of oxygen gas accumulated in closed body cavities can lead to mechanical stress on hollow organs and even perforations. But oxygen solubility in blood can also cause venous or arterial gas embolism in central nervous system or less likely in portal vein[6]. Oxygen embolism could be also caused by entry of hydrogen peroxide to open vessels during orthopedic surgery [12]. There are at least three mechanisms of oxygen gas embolization due to hydrogen peroxide. Firstly, requires a patent foramen ovale. Oxygen bubbles are formed in or brought into right atrium then they move to left atrium which will result as a arterial oxygen gas embolization. Secondly, pulmonary aspiration of hydrogen peroxide can cause direct arterial oxygen gas embolization. Thirdly, undissociated hydrogen peroxide absorbed in the gastrointestinal system may catalyse in the arterial circulation after crossing the lung, leading to arterial oxygen gas embolization [1]. In most cases there is no evidence of embolization in MRI although neurological symptoms are present [7]. Consequences of inhalation exposures appears to be mild, mostly coughing and transient dyspnoea if the concentration was low. Expect those not dangerous symptoms, severe irritation and inflammation of mucous membranes can occur after inhalation of highly concentrated solutions [6].

Lipid peroxidation is the oxidative degradation of lipids that consists of three major steps: initiation, propagation, and termination. The chemical products of this oxidation are known as lipid peroxides or lipid oxidation productsmodify cellular membranes by lowering the hydrophobicity of the lipid part of membranes, depolarisation of the membrane and disturbing the lipid asymmetry of the membranes. They also inhibit the activity of the

membrane enzymes and transport proteins [13]. This mechanism is seen during haemolysis by rupturing red blood cell due to phototherapy [14]. In addition, end-products of lipid peroxidation may be mutagenic and carcinogenic [15]. The risk of esophageal carcinoma (adenocarcinoma and squamous cell carcinoma) increases 1000-3000 times after caustic ingestion. Carcinogenesis is often observed in area of anatomic narrowing and could depend on increased exposure to caustic substance. Bypass surgery does not ward off esophageal neoplasms [16].

Diagnosis

There are several rules of dealing with the patient after caustic liquid ingestion. In case of positive history we must always suspect damage of gastrointestinal tract even in the absence of symptoms. Endoscopic examination confirmed, that less than half patients with lesions in digestive tract present symptoms. Intake of different substances (ethanol, phenol, psychotropic medicines) can mask feeling pain and other symptoms [2]. It is important to remember about possibility of occurrence damage of upper respiratory tract such as larynx or vocal cord injury. Due to this damages we can observe dyspnoea and difficulties with breathing. Therefore, it is recommended to ask for laryngological consultation.

The main purpose of diagnosis is to found patients with dangerous damages to gastrointestinal tract without carrying out unnecessary procedures and hospitalisations. In case of suspicion bleeding nasogastric tube is often assumed. It is good way to confirmed bleeding, decompression stomach and control dynamics of bleeding. The use of this method is controversial because if we do not do gastrofiberoscopy before we would cause iatrogenic damages. Suspicion of perforation thorax and abdomen anterior-posterior (AP) x-ray should be done [2]. Sensitivity of AP x-ray examination is not very high but the possibility of increasing this has been reported by doing lateral projection x-ray. In several publications we can found that performing x-ray with contrast confirms the occurrence motor dysfunction but it does not affect on recognizing perforation. Running x-ray with contrast brings a risk of aspiration into respiratory system [2]. X-ray with using barium sulfate contrast could be useful in later stage to found stenosis and deformation of gastrointestinal tract. Greater sensitivity of detection perforation using computed tomography (CT) with contrast than x-ray has been reported. The most useful diagnostic procedure is gastrofiberoscopy, we can make it after exclusion perforation [2]. It should be done in max 2 days after exposure to every stable patient, due to the fact that symptoms do not correlate to grade of damage [2,17]. There is no single symptom which could recognize all patients with damage of gastrointestinal tract [18]. Because of intensive demarcation necrotic tissue between 8 and 14 day after exposure, it is not recommended to do gastrofiberoscopy due to high risk of perforation and bleeding [2].

Indications for gastrofiberoscopy are:

- Every patient with positive history of ingestion caustic substance, even without symptoms;
- Every patient after suicide attempt;
- Every patient after unintentional consumption with symptoms;
- Child with emergency symptoms.

Mucosal damage is graded using a modified endoscopic classification described by Zargar (table S3) [19].

Table 3. Zargar's scale

Grade	Description
0	Normal mucosa
1	Edema and hyperemia of the mucosa
2a	Hemorrhage, erosions, blisters, superficial ulcers, without stenosis
2b	Grade 2a plus deep discrete or circumferential ulcerations
3a	Small scattered areas of multiple ulceration and areas of necrosis with brown-black or greyish discoloration
3b	Extensivenecrosis

Zargar's scale facilitates proceedings and reduces the risk of mistake. Patient with grade 1 or 2a if he could eat normally, can be discharged. This grade do not carry any risk of early and late complications from gastrointestinal tract. In grade 2b risk of complications raise to 70%, grade 3b has the highest risk of perforation and this patients should be hospitalized [2,20]. Burns caused by caustic substance are similar to thermal burns – there is increased catabolism with protein deficiency which impede mucosal healing and higher risk of infection [2].

Because of possibility of occurrence symptoms from upper respiratory tract such as larynx or vocal cord injury, it is recommended to ask for laryngological consultation.

Pharmacological treatment

There are several rules of treatment patient after caustic substance ingestion that need to be followed. Information on type of substance, volume and time of ingestion should be collected. At first you should proceed according to ABC to secure basic life functions. Decontamination of body shells should be done by using lots of water. It is not recommended to:

- Provoke vomiting to avoid secondary exposure of esophagus.
- Giving active carbon because it do not absorb caustic substance and can stimulate vomiting.
- Giving neutralizing agents because neutralizing reaction is a exothermic reaction which emits heat that can be additional damaging factor.
- Do not do gastric lavage. It is acceptable only in ingestion of acids [2].

Steroids

Using steroids is recommended only in 2 grade in Zargar's scale mucosal damage. Steroids inhibit transcription of procollagen, fibronectin, transforming growth factor β (TGF-β), cytokines and reduce synthesis of collagenase inhibitor - α2-macroglobulin, but it can mask infection and increase a risk of thromboembolic complications [2,21]. Steroid therapy is recommended only in grade 2 in Zargar's scale because of high risk of strictures formation. In those cases steroids should be given in 1-2 days from the exposure. In first 2-3 weeks steroids should be administrated intravenously and then orally with gradual dose reduction within the next month [2]. Steroids are not recommended in patients with severe burns [22].

Antibiotics

The main role of antibiotics is to prevent infection of intestinal bacteria, caused by damage of intestinal barrier. In case of infection antibiotics supress healing and fibrosis initiated by infection [2].Antibiotics should be given if there is perforation, infection or in case of use steroids. Animal experiments have shown that using antibiotics and steroids in

early stage of ingestion reduce risk of creating strictures [21]. There is no indications for using antibiotics prophylaxis if we do not use steroids [16].

Protecting mucosal membrane

It should be consider to use meds protecting mucosal membrane such as sucralfat, bismuth compounds, proton pump inhibitors (PPI) and H_2 blockers [20]. Sucralfat increase secretion of HCO^{3-} and PGE_2, decreases secretion of pepsin and bile acids. Bismuth compounds also increase secretion of HCO^{3-} and PGE_2 but also have antibacterial effect. H_2 blockers and PPI decrease odynophagia but do not protect from formation strictures [2] .

Antihistamines

Antihistamines can inhibit disturbing of perfusion mucosal and submucosal. It prevents effect of histamine release from mastocytes [2].

Stricture prevention

Treatment which supresses fibrosis is not well understood. Animal experiments have shown that using β-aminopropionitrile, colchicine, penicillamine has beneficial effect by tearing off bonds collagen fibers. Similar activities confirmed by using N-acetylcysteine, interferon ɣ, epidermal growth factor. Also octreotide, interferon-alfa-2b and cytokines depress the fibrotic activity [16]. Could be consider to use anti-oxidant therapy using vitamin E, mast cell stabilizer and phosphatidylcholine because of inhibit collagen production [23,24]. It has been reported that using mitomycin C (replication of deoxyribonucleic acid (DNA) inhibitor) in topically injection to the esophageal mucosa, may be useful in preventing stenosis [16]. Also an animal model revealed that using the heparin can reduce the risk of formation of strictures [2].

Nutrition

During the treatment of patient that was exposured to caustic substances it is highly important to nourish the patient enough for his increased need. It is related not only to direct irritation and damage of gastrointestinal tract but also increased catabolism. This situation is similar to thermal burns. Those patients have higher caloric demand. In cases of damage classified as 1 and 2A it is recommended to start oral nutrition on second day provided that the patient is able to swallow and tolerates meals. The diet should be liquid/semi-liquid and expanded gradually. 2B and 3 grade damages require use of a Sengstaken–Blakemore tube [2]. In cases of increased catabolism the diet should be expanded on parental nutrition.

Endoscopic and surgical treatment

Esophageal dilatation is another form of treatment, it is therapeutic endoscopic procedure that enlarges the lumen of the esophagus [25]. There are two kinds of endoscopic treatment depending on whether an esophageal stricture is already present. Early treatment means widening esophagus with stents (right after the exposition before the formation of stricture). This method is rarely used and not so recommended due to the risk of perforation and bleeding. Moreover, it stimulates fibrosis. Second kind of treatment is used after the formation of stricture. It can be started after 2-4 weeks from diagnosing the stricture. Initially esophageal dilatation is repeated every week gradually extending time between following sessions. The aim is to obtain diameter >15 mm [2]. Nevertheless, 10-50% of esophageal strictures can not be widened. Worse prognosis are for strictures that arise quickly, cover a long section of the esophagus, strictures with thick wall (assessment in CT) or the non-concentric ones. Another point is that patients tolerate this kind of treatment badly. Expect of the perforation and bleeding there are other complications like sepsis or abscess. During the treatment and between the sessions acid suppression therapy and prophylactic antibiotic therapy are recommended [2].

There is lack of clear criteria about surgical treatment in the early stage of damage. Surgical treatment is using in case of suspicion of perforation, transmural necrosis to avoid perforation and in treatment of stenosis. Surgical methods are used when stenosis can't be extended by endoscopic procedures [2]. There are two kinds of surgery (in the later stage of stenosis):

- First is resection of the esophagus with reconstruction from the stomach, small intestine or colon.
- Second type assumes leaving the esophagus, but is also related with still present reflux and possibility of other complications [2].

Patients with symptoms of perforation need immediate laparotomy [2,16]. Some authors suggest laboratory and endoscopic criteria for emergency surgery such as disseminated intravascular coagulation, renal failure, third degree of esophageal burns [16,26,27].

Summary

Hydrogen peroxide could be dangerous substance if it is not stored the right way. Usually, exposures for hydrogen peroxide are with 3% solution and are oligosymptomatic or even asymptomatic [5]. However, patient after exposure to >30% hydrogen peroxide should receive a complex treatment. Physicians need to be alert to the symptoms of not only gastrointestinal tract but also CNS. Patient exposured to caustic substance is an interdisciplinary patient. It is very important that many specialists such as toxicologist, surgeon, laryngologist, gastroenterologist and dietician to cooperate. Despite complex treatment, many patients may still need control in clinic for several months. Exposure for caustic substance in children may have serious impact for their development process due to applied treatment – especially steroids and surgical interventions such as reconstruction of gastrointestinal tract and can have consequences for their entire life. Therefore, treating those patients may be challenging, requires the highest attention and specialist care.

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