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Spectrum of sodium hypochlorite toxicity in man—also a concern for nephrologists

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Abstract
Sodium hypochlorite (NaOCl) is the active ingredient in household bleach and is a very common chemical. It has been used in medical and commercial situations dating back to the 18th century for its disinfectant properties, including topical use in medicine as an antiseptic. For this indication, NaOCl is a proven and safe chemical. However, exposure of NaOCl beyond topical use, whether it is intentional or accidental, is associated with significant risks due to its strong oxidizing properties. Potentially damaging scenarios include ingestion, inhalation, deposition into tissue or injection into the bloodstream. All of these scenarios can lead to significant morbidity and even mortality. In this review, we examine the toxicity associated with NaOCl exposure and analyze potential mechanisms of injury, placing special emphasis on the potential for renal toxicity. Due to the extreme ease of access to household bleach products and its use in medicine, it is important for the clinician to understand the potential damage that can occur in NaOCl exposures so that complications can be prevented before they arise.

Keywords: acute kidney injury; bleach; NaOCl systemic toxicity; sodium hypochlorite

Introduction

NaOCl, the active ingredient in household bleach, is an extremely useful disinfectant and potentially dangerous chemical that has been utilized in medicine and by industry since the 18th century. Claude Louis Berthollet, a French chemist, was the first to isolate and manufacture hypochlorite in 1789 using laboratory techniques. In the 19th century, a Hungarian obstetrician, Ignaz Semmelweis, found that the rate of puerperal sepsis could be reduced dramatically by enforcing hand washing with hypochlorite before delivery. Hypochlorite was again found to be extremely useful on a large scale during World War I. Wounds suffered by soldiers often became infected through contamination with soil and excrement resulting in a high rate of amputations and infections resulting in death. A chemist named Henry Dakin was commissioned to solve the high rate of wound infection complications among injured soldiers. Dakin developed a buffered solution of sodium hypochlorite at concentrations of 0.45–0.5%, which was non-irritating while preserving its antiseptic properties [1]. Today, Dakin's solution continues to be used by wound care units and clinics around the world. As these historical anecdotes illustrate, NaOCl has made a significant impact on medicine and is used routinely in the treatment of burns, wounds, ulcers and as an antiseptic in dentistry.

The industrial application of NaOCl is common and has wide uses ranging from textile cleaning to water purification. Furthermore, bleach-containing products are nearly universal in modern homes. Although NaOCl has extremely low toxicity in the concentrations used for medical disinfection, it is often sold in concentrated solutions meant for dilution commercially. At these high concentrations, there is a significant potential for toxicity. Thus, awareness about NaOCl's potentially deadly properties is critically important for those who may suffer from exposure and the health care providers who will care for them. In this review, we will examine the toxicity associated with NaOCl exposure and analyze potential mechanisms of injury. We will place special focus on the renal toxicity potential of NaOCl.

Pharmacology of hypochlorite

NaOCl is a chemical compound consisting of sodium, oxygen and chlorine. It is manufactured using by bubbling chlorine gas into sodium hydroxide (NaOH) to form equal amounts of NaOCl and NaCl. Typical concentrations found in commercial bleach products range between 3 and 5% solution with an approximate pH of 11 [2]. Mixed with water, NaOCl combine to generate highly reactive hypochlorous acid (HOCl), conferring its potent antibacterial and antifungal properties. Hypochlorous acid generates superoxide radicals that cause oxidative injury and cell death. Single-dose toxicity studies in rats using 1.1% NaOCl solutions were also done to establish the LD_{50} of the chemical (LD_{50} is the dose required to be

lethal in 50% of tested animals). The LD_{50} was calculated to be 290 mg/kg of an oral dose and 33.3 mg/kg of an intravenous dose [1].

Route of exposure and toxicity

Dermal injury

When NaOCl is applied topically, there is no published evidence of systemic toxicity and local reactions have not been reported to be life-threatening [1]. Dermal toxicity studies performed in rodents and rabbits by exposing shaved skin to 1.1% NaOCl solution, showed no signs of significant local irritation after 14 days of testing. Guinea pigs examined for inflammatory response to subcutaneous exposure to NaOCl at low concentrations showed no significant difference in local inflammatory response in any of the sites when compared to those treated with normal saline [3]. However, single-dose studies performed on animals using higher concentrations have found toxic reactions to intradermal injections. In a study by Pashley *et al.* [2], intradermal injection of 5.25% NaOCl produced immediate hemorrhage and edema lasting hours after injection. These findings demonstrate the varying toxicity of NaOCl depending on the route of administration and concentration. It is important to note that in many of these studies, low concentrations were studied because of how it is used in medicine. In commercial and industrial situations, bleach is found in much higher concentrations and is likely to produce more damage.

Muscle and soft tissue injury

Despite NaOCl's very safe profile when used topically, it can sometimes be injected beyond the dermis and into soft tissue causing iatrogenic injury. This most often occurs in endodontics, where sodium hypochlorite is used as an irrigant of the root canal system. When this occurs, it can lead to severe tissue reactions characterized by pain, swelling, hemorrhage and potentially secondary infection or lasting paresthesia [4]. If the area becomes secondarily infected by pathogenic flora, there is a risk for sepsis and endocarditis.

Local injection of a large amount of concentrated NaOCl into soft tissue could cause significant muscle breakdown, releasing muscle contents that can lead to acute kidney injury (AKI) via rhabdomyolysis. Myoglobin, the oxygen-binding protein found in muscle tissue, is freely filtered by the glomerulus and is metabolized by tubular cells that take up the protein via endocytosis [5]. Myoglobin is inherently nephrotoxic. Other factors contributing to rhabdomyolysis-induced AKI include severe hypovolemia and tubular obstruction [6]. Hypovolemia results from the necrosis and inflammation at the site of injection or injury that causes a loss of intravascular volume via a 'third space' effect. The subsequent decrease in effective arterial blood volume can lead to pre-renal AKI. Acidosis frequently is associated with such injuries due to the release of large amounts of sulfur-containing proteins that can lead to a metabolic acidosis. To excrete this acidic load, the kidney acidifies the urine that triggers the precipitation of filtered myoglobin when it interacts with the Tamm-Horsfall protein [5]. These myoglobin precipitates cause obstruction of tubules within the kidney, specifically in the distal tubules that contributes to AKI. When the urine becomes more acidic, below pH 5.6, myoglobin dissociates into two proteins: ferrihemate and globin. Ferrihemate is directly nephrotoxic, causing tubular injury and leading to acute tubular necrosis (ATN) [6]. It is important to note that there is an extremely low risk of rhabdomyolysis following deposition of NaOCl into soft tissue because these injections are usually of small volume. While there have been no recorded cases of rhabdomyolysis following injection of NaOCl into soft tissue, the possibility remains if a large enough dose is given due to the compound's ability to cause necrosis in high concentration.

Gastrointestinal toxicity

Ingestion of corrosive substances, such as strong alkali bases, often produces severe esophageal burns and necrosis. Although NaOCl is a strong alkali, bleach ingestions typically cause minor damage to the esophagus, causing first-degree burns with hyperemia and edema of the mucosa. Indeed, ingestions of bleach rarely cause complications sometimes seen in more severe esophageal trauma such as stenosis, strictures or perforation. It is nevertheless a significant public health problem because bleach ingestions are common due to the availability of household bleach compared to other chemicals. Recommendations for treating first-degree esophageal burns by bleach ingestion include observation and conservative management [7–10]. However, there are occasional case reports of esophageal stenosis and stricture formation following ingestion of sodium hypochlorite [8]. Large volume ingestion of bleach, typically associated with suicide attempts, can result in disastrous complications including death [9,11]. In one such case, a 66-year-old female ingested a large quantity of household bleach (sodium hypochlorite 5.25%) and presented with severe esophageal and airway burns along with perforation of the gastroesophageal junction, bilateral pneumothorax and pneumoperitoneum. The case was complicated by severe metabolic acidosis and cardiopulmonary arrest, which resulted in the woman's death [11].

Long-term complications of chemical ingestion can include esophageal stricture formation, which typically develops between 3 and 8 weeks after ingestion-related burns [7]. Stricture formation can lead to poor oral intake in patients recovering from ingestion, especially those that are refractive to dilatation. These patients can suffer from malnutrition and dehydration and may require enteral or parenteral nutritional support.

Pulmonary toxicity

Patients who ingest bleach often have damage to the respiratory tract as well as the esophagus. The damage may be due to inhaled vapors of bleach or could be related to aspiration during ingestion or vomiting afterward. If severe, a patient with respiratory tract damage may require intubation and mechanical ventilation for respiratory

distress or acute respiratory distress syndrome (ARDS). Mechanical ventilation with ARDS can lead to AKI by different mechanisms including hypoxemia, hypercapnia, barotrauma-induced inflammatory response and hemodynamic changes well described by Kuiper *et al.* [12].

Hematologic toxicity

NaOCl breaks down into water and hypochlorous acid immediately when it is mixed with plasma. Hypochlorous acid then induces hemolysis almost immediately through membrane protein modification [13]. Experiments have shown that hypochlorite produces visible hemolysis at various concentrations in <1 min [14].

Renal toxicity

Direct damage to the kidney following ingestion of NaOCl has not been described though esophageal burns have been associated with renal insufficiency [15]. In severe cases such as those described above, there are many potential situations that would precipitate renal damage that are important to keep in mind when treating these patients. In cases of perforation, the contaminated esophageal mucosa is opened into the mediastinum, thorax or peritoneal cavity that allows oral bacteria to seed these spaces. This can lead to systemic inflammatory response syndrome (SIRS), sepsis or eventually to septic shock. In these cases, diffuse systemic vasodilatation results in poor renal perfusion and AKI. Acute renal failure occurs in 19% of patients with moderate sepsis and up to 51% of patients with septic shock. This is significant because the combination of acute renal failure with sepsis approaches 70% [16]. In SIRS or sepsis, cytokine release triggers upregulation of the inducible form of nitric oxide synthetase, releasing nitric oxide from endothelium and causing systemic arterial vasodilatation. As systemic vascular resistance decreases, baroreceptors trigger the activation of neurohormonal axis including the rennin-angiotensin-aldosterone system (RAAS). The activation of RAAS is required to maintain adequate systemic blood pressure; however, the effect on the kidney is that of vasoconstriction which predisposes the patient to AKI [16]. NaOCl ingestion can also cause significant nausea and vomiting, which may lead to volume depletion and pre-renal AKI in the patient who is not adequately volume repleted.

The evidence that hemolysis can cause both AKI and chronic kidney disease (CKD) is well established. CKD is often seen in patients with conditions that produce hemolysis such as paroxysmal nocturnal hemoglobinuria or cardiac valvular disease [17]. In these conditions, hemosiderin deposits can be seen on renal biopsies in those with CKD. During hemolysis, hemoglobin is released into the plasma where it binds to haptoglobin and is taken to the reticuloendothelial system to be broken down. With the release of too much hemoglobin at once, haptoglobin stores are saturated and free heme proteins are filtered by glomeruli. Heme proteins can cause AKI via three mechanisms: decreased renal perfusion, direct cytotoxicity and intratubular cast formation [17]. The cytotoxic effects of heme proteins are due mainly to their oxidative and proinflammatory properties. Heme can oxidize lipid including cell membranes, denature proteins and destroy the cytoskeleton. The mitochondria are most affected by heme proteins, which impair mitochondrial respiration to the point of complete cessation of oxygen consumption. Heme can also be cytolytic by activating and inducing cell-damaging enzymes like caspases and cathepsins [18].

Renal tubular cells do have a system to catabolize intracellular heme to prevent oxidant damage—the heme oxygenase (HO) system. HO-2 is a consititutive enzyme present minimally at all times in renal tubular epithelium, while HO-1 is an inducible enzyme that is expressed in times of stress or in an abundance of heme [18]. This system can be overwhelmed; however, and with large amounts of intradermal or smaller amounts of intravenous NaOCl exposure, one can see how the hemolysis produced can lead to AKI or failure. In order to have a direct cytotoxic effect on renal tubular cells, NaOCl must be present in the renal vasculature. However, as noted previously, NaOCl instantly generates hypochlorous acid when mixed with plasma. Hypochlorous acid then generates chloramines and reactive oxygen species (ROS) that are used in the neutrophil reaction. While NaOCl does not have a direct cytotoxic effect on renal tubular epithelium, its breakdown products may. Most of the research involving HOCl and its potential effects on the kidney are related to the myeloperoxidase reaction and inflammatory cells that use the compound. While this does not directly correlate with a potential exogenous source of hypochlorous acid, the inflammatory release of HOCl is likely a good model for a potential load of sodium hypochlorite in the bloodstream.

Hypochlorous acid may oxidize or modify proteins that may be taken up by tubular epithelial cells. There is evidence that these HOCl-modified proteins may be directly cytotoxic to tubular epithelium and contribute to tubular epithelial damage and AKI [19]. It is also likely involved in CKD such as degenerative and immunologic disorders from the myeloperoxidase reaction [20].

Hypochlorous acid produces reactive oxygen species during its reactions with proteins and lipids, which are likely damaging to the kidney. The healthy kidney does generate small amounts of ROS during its normal oxidative respiration. However, larger amounts of ROS can contribute to both the progression of chronic renal disease or AKI, usually in the form of ATN [21]. The ROS that are most commonly seen in renal disease are the superoxide anion, hydrogen peroxide and the hydroxyl radical, which is the most volatile. These damage the renal tubular epithelium via peroxidization of lipids in the cellular membranes, oxidizes enzymes and proteins to alter their function within the cell's metabolism and destabilize the structural cytoskeleton of the cell [21]. Thus, the ROS generated by hypochlorous acid can lead to both AKI in the form of ATN and also contribute to existing renal disease. This may be an additional mechanism by which exposure to sodium hypochlorite can lead to AKI, especially in circumstances of accidental injection, which can strike blood vessels.

Table 1. Sodium hypochlorite effects based on type of exposure and relation to AKI

Topical		
Wounds	Local inflammation	Extremely low toxicity when used topically in a dilute form. No published evidence of systemic toxicity or severe local reaction.
Ingestion		
Esophagus	Nausea/ vomiting	Significant vomiting may lead to volume depletion and pre-renal AKI.
	Burns	Typically causes minor, first-degree burns of esophageal mucosa. Occasional rare case reports of more significant injury in large volume or high concentration ingestions.
	Perforation	Extremely rare. Isolated reports of large quantity ingestions causing perforation. SIRS, sepsis and septic shock are possible, leading to AKI.
	Stricture	Occasional reports of stricture following bleach ingestion. More common in more caustic ingestions. Typically seen 3–8 weeks after ingestion. May result in poor nutritional intake and hypovolemia that may precipitate AKI.
Stomach/ intestine	Inflammation	No evidence to support.
Inhalation/aspiration		
Respiratory tract	Burns	May occur due to inhalation of vapors. Damage to respiratory tree may induce acute lung injury (ALI) and respiratory distress requiring mechanical ventilation. Pulmonary edema or ARDS can lead to AKI via severe hypoxemia and hypercapnia by decreasing renal perfusion and increasing renal vascular resistance.
	Aspiration	Aspiration of vomited gastric contents including hypochlorite may induce further burns, respiratory damage or aspiration pneumonia.
	Respiratory failure	Respiratory failure requiring mechanical ventilation can cause AKI as above. Increased risk of pneumonia leading to SIRS or sepsis. Ventilator-induced barotrauma may induce AKI through hemodynamic changes of released inflammatory molecules. Ventilation-related hemodynamic changes reducing cardiac output may lead to AKI.
Injection		
Soft tissue	Tissue breakdown	Large amounts of muscle breakdown as a result of injection may lead to rhabdomylolysis. Potential AKI secondary to direct nephrotoxicity of free myoglobin, severe hypovolemia and tubular obstruction from myoglobin precipitates.
	Infection	Infection of damaged soft tissue can lead to SIRS or sepsis that may induce AKI.
Blood	Hemolysis	Severe anemia may lead to reduced cardiac output and oxygen delivery to the kidney leading to AKI. Free heme proteins in circulation can cause decreased renal perfusion, direct cytotoxicity and intratubular cast formation.
	Oxidant	If injection is severe enough, hypochlorous acid may oxidize or modify proteins to create ROS, potentially contributing to AKI and chronic kidney disease. Oxidized proteins in bloodstream may be taken up by tubular epithelial cells, inducing cellular injury.

Conclusion

In the USA, NaOCl is used in the medical profession as a topical antiseptic in many applications such as burns, ulcers or for cleaning the root canal system in endodontics. When used in this fashion, its toxicity is extremely low, a fact that has been proven with animal models as well as being observed in humans over time. However, sodium hypochlorite is an extremely accessible chemical and can be found in higher concentrations than used medically in nearly every home. It is this ease of access that makes understanding the potential implications of NaOCl exposure so important. When a patient presents with bleach ingestion, for example, one should know of the potential damage that can occur in such a circumstance so that complications can be prevented before they arise (Table 1). For this reason, it is important for health care professionals including physicians to understand the potential ways that NaOCl or similar chemicals can lead to kidney injury. In its indicated modality of topical application, no significant systemic toxicity has been found. However, oral or intravenous systemic exposure to NaOCl can have organ-specific toxic effects.

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