Review Article

SAFE USE OF HYDROGEN PEROXIDE AS A NASAL SPRAY - A REVIEW

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ABSTRACT

The present review aims to find out the possibility of using a H_2O_2 nasal spray by studying the available hydrogen peroxide sprays for human use for various purposes. Normally 3-6% solutions of H_2O_2 are used in medical applications. The reported NOEL and LOAEL studies indicated that up to 14.6mg/m^3 was found to be safe in human trials. Hence the available safety reports recommend that, a single exposure of 0.3% H_2O_2 in the external nostrils as a nasal wash with a subsequent blowing of nose can be helpful in relieving decongestion.

Keywords: Hydrogen peroxide, nasal wash. 0.3% H_2O_2

1.INTRODUCTION

Hydrogen Peroxide is a colourless liquid at room temperature possess powerful oxidizing activity[17]. Aqueous solutions of 3%-6% are used for cosmetic & medical applications. Hydrogen Peroxide and water do not form an azeotropic mixture (two or more liquids whose proportions cannot be altered or changed by simple distillation), and are completely separable[18].

Hydrogen peroxide is physiologically produced by oral bacteria and plays a significant role in the balance of oral microecology due to its important antimicrobial activity [(1)]. In the epithelial cells, the enzyme superoxide dismutase catalyses a reaction leading from hydrogen peroxide to superoxide. The oxidative stress stimulates a local innate response through activation of the toll-like receptors and the NF-κB[2]. Viral infections also activate these kinds of reactions [(3)]. Virus-induced oxidative stress plays an important role in the regulation of the host immune system and the specific oxidant-sensitive pathway is one of the effective strategies against viral infections [4-6]. Many viruses have been found to be sensitive to hydrogen peroxide, such as swine flu, rubella, rabies etc[7-12].

Hydrogen Peroxide is used in cosmetic sprays and could possibly be inhaled; for example, it is reported to be used up to 4% in aerosol hair sprays. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 µm, with propellant sprays yielding a greater fraction of droplets/particles < 10 µm compared with pump sprays [(13,14)]. Thus, most droplets or particles incidentally inhaled from cosmetics would be deposited in the nasopharyngeal and thoracic respiratory tract regions and would not be inspired (i.e., they would not enter the lungs) to any appreciable amount [(15,16)].

This study aims at determining the possibility of usage of Hydrogen Peroxide as a nasal wash at safe concentrations.

Pharmacokinetics of H_2O_2

Hydrogen Peroxide is a normal metabolite in aerobic cells[19]. Hydrogen Peroxide passes readily across biological membranes. Under normal, physiological conditions, the concentration of Hydrogen Peroxide in tissues is 1 to 100 nM/L (0.034 to 3.4 µg/L) depending upon the organ, cell type, oxygen pressure, and cell metabolic activity [(20)]. In biological systems, Hydrogen Peroxide is metabolized by catalase and glutathione peroxidases [(20)].

The highest activities are found in highly vascularized tissues such as the duodenum, liver, kidney, and mucous membrane [(21)]. In the metabolism of Hydrogen Peroxide to water and oxygen, the decomposition rate in human plasma is approximately 0.01 to 0.05 M/L/min. Catalase is more efficient at the decomposition of higher concentrations of Hydrogen Peroxide; glutathione peroxidase is more efficient at decomposing lower Hydrogen Peroxide concentrations [(22)]. Glutathione peroxidase is present in cytosol and mitochondria but not in peroxisomes. A high glutathione peroxidase reduction activity of Hydrogen Peroxide is found in liver and erythrocytes; moderate levels are found in the heart and lungs, and a low activity is present in muscle. In the presence of transition metals in cells, Hydrogen Peroxide can be reduced via the Haber-Weiss reaction [(23)]. This reaction produces hydroxyl radicals (free radicals) which are highly reactive and can result in lipid peroxidation. At high uptake rates, Hydrogen Peroxide can pass the absorption surface and enter the adjacent tissues and blood vessels, where it is rapidly degraded by catalases and molecular oxygen is liberated [(19,20)]. As a consequence of this, mechanical pressure injury and oxygen embolism may be observed. In the view of the high degradation capacity for Hydrogen Peroxide in blood, it is unlikely that it is systemically distributed; therefore, the endogenous steady state levels of the substance in tissues are unlikely to be affected. On 1000-time dilution of the rat blood, the half-life of Hydrogen Peroxide was less than 5 min at both 5 and 10 mg/L. 6 For 20

mg/ml, the half-life was more than 4 h. In the study, concentrations of Hydrogen Peroxide were much greater than the range of aqueous solutions in products or in-use concentrations. Furthermore, this supports the view of rapid decomposition of Hydrogen Peroxide entering the blood circulation which will not be systemically available. For this reason, the distribution of Hydrogen Peroxide in the body is expected to be very limited after exposure to Hydrogen Peroxide solutions. Due to the rapid endogenous transformation into water and oxygen, there is no specific excretion of Hydrogen Peroxide or a determinable degradation product [20].

2. METHODOLOGY

2.1. Mucolytic Action of H_2O_2

In 1941, William et al. [33] demonstrated the mucolytic properties of hydrogen peroxide and ascorbic acid on purified gastrointestinal mucin [30]. They showed that hydrogen peroxide as a single agent is capable of degrading mucin and that the speed of the reaction can be increased 250-fold by the addition of ascorbic acid (equimolar quantities). Hydrogen peroxide is an oxidizing agent that may target the disulphide bonds and hence disrupt the cross linkage between adjacent molecules [33]. It may also attack the glycosidic linkages [35].

A study by Pillai et al in 2012 compared both ascorbic acid (0%–0.2%) and hydrogen peroxide (0%–3.0%), as single agent which showed mucolytic action on Peritoneal mucin. A linear increase in mucolysis has demonstrated with increasing concentration of each agent [36].

2.2. Inhalation

Anesthetized rabbits (number and strain not specified) were administered aerosolized 1% to 6% aq. Hydrogen Peroxide by inhalation. The left atrial blood was found to be supersaturated with oxygen up to levels that corresponded to oxygen administration at 3 atm. When the amount of Hydrogen Peroxide was increased, small bubbles began to appear in the blood samples. The amount of arterial oxygen was the same with both 1% and 6% Hydrogen Peroxide. No further details were provided [19].

2.3. Toxicokinetic Studies in human trials

A study by Ernst Gard et al depicts that Subjects (n = 11) were exposed to Hydrogen Peroxide (30% aq.; 0, 0.5, and 2.2 ppm; calculated as 0, 0.7, and 3.08 mg/m3) vapours for 2 h at rest in an exposure chamber (20 m3). Symptoms related to irritation and central nervous system (CNS) effects were rated with Visual Analog Scales. The ratings varied considerably but were generally low and with no significant differences between exposure conditions, although the ratings of smell, nasal irritation, and throat irritation showed borderline tendencies to increase at 3.08 mg/m3 , but not at 0.7 mg/m3 . Nasal airway resistance increased after exposure to 3.08 mg/m3 , but not at 0.7 mg/m3 . No effects in relation to the exposure on pulmonary function, nasal swelling, breathing frequency, and blinking frequency were detected. No clear effects were seen on markers of inflammation and coagulation (e.g., interleukin-6, C-reactive protein, serum amyloid A, fibrinogen, factor VIII, von Willebrand factor, and Clara cell protein in plasma). The authors concluded that Hydrogen Peroxide was slightly irritating at 3.08 mg/m3 , but not at 0.7 mg/m3 [24].

Another study by National Industrial Chemicals Notification and Assessment Scheme (NICNAS) towards Human health, Tier II assessment for hydrogen peroxide (H2O2) in 32 subjects indicates the threshold of detection for irritation through inhalation exposure was 10 mg/m3 (independent of the exposure time, which was from 5 minutes to 4 h) when Hydrogen Peroxide (concentration not provided) vapor was inhaled through the nose using a face mask [25].

2.4. Short Term Inhalation Toxicity Study

Mice exposed to Hydrogen Peroxide (90% aq.; 79 or 107 mg/m3) for 6 h per day for 2 to 3 days per week, for up to 4 weeks had nasal discharge, oedematous feet, and irritation of the skin at week 2 and hair loss around the nose (probably due to scratching due to irritation) at week 5; seven of nine mice died after eight exposures in the low-dose group, and in the high dose group, five of 10 mice died after eight exposures and eight of 10 died after 18 exposures[26].

Rats exposed to Hydrogen Peroxide (50% aq.) 5 days per week, 6 h per day, for 28 days showed clinical signs at 14.6 mg/m3 (including reddened nose, salivation, irregular breathing), but not at 2.88 mg/m^3; the no-observed-effects-level (NOEL) was 2.9 mg/m^3 and the Lowest Observed Adverse Effect Level (LOAEL)[2] was14.6mg/m^3. Rats exposed to 93 mg/m3 Hydrogen Peroxide (90% aq.) for 6 h per day for 2 to 5 days per week for 7 weeks (30 exposures) showed signs of nasal irritation and profuse discharge at 2 weeks, lung congestion and hair loss (probably due to scratching due to irritation) at 5 weeks [26]. In black rabbits exposed to 90% Hydrogen Peroxide (30 mg/m3) vapor for 6 h per day, 5 days per week for 12 weeks, there were no effects observed except for the bleaching of the fur and some irritation around the nose[26].

2.5. Sub-Chronic Inhalation Toxicity Studies

In rats exposed to Hydrogen Peroxide (concentration not specified) in whole body chambers for 5 h per day, 5 days per week for up to 4 months, the threshold for lung effects was 10 mg/m3 ; the NOEL was 1 mg/m3 and the LOEL was 10 mg/m3 . 2,32 There were no mortalities when rats were exposed to Hydrogen Peroxide (50% aq.) up to 10.3 mg/m3 for 6 h per day, 5 days per week, for 13 weeks; the NOAEL was 3.6 mg/m3 for male and female rats for decreased liver and thymus weights.2

Irritation was noted around the nose of rabbits exposed to 90% aq. Hydrogen Peroxide at 22 ppm (calculated as 30.77 mg/m3) for 3 months[27].

2.6. Chronic Toxicity Inhalation Studies:
In two dogs exposed to aerosolized 90% Hydrogen Peroxide (10 mg/m^3) for 6 h per day, 4 to 5 days per week for 26 weeks, the only observed effects were fur bleaching and loss at 14 weeks, and sporadic sneezing and lacrimation at 23 weeks [26]. At necropsy at 26 weeks, the lungs had areas of atelectasis and emphysema, and there was some hyperplasia in bronchial musculature [26].

2.7. Carcinogenicity Studies:
International Agency for Research on Cancer (IARC) determined that there is inadequate evidence in humans to come to a conclusion on the carcinogenicity of Hydrogen Peroxide and that there is limited evidence in experimental animals on the carcinogenicity of Hydrogen Peroxide. IARC concluded that Hydrogen Peroxide is not classifiable as to its carcinogenicity to humans (Group 3)[28].

2.8. Other Occupational Exposure Studies on H_2O_2:
The Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for inhalation of Hydrogen Peroxide is 0.0001% (1.4 mg/m3) averaged over an 8-h work shift. The National Institute for Occupational Safety and Health (NIOSH) immediately dangerous to life or health (IDLH) level for Hydrogen Peroxide is 0.0075% and the recommended exposure limit (REL) is 0.0001% (1.4 mg/m^3) [29,30]. According to the American Industrial Hygiene Association (AIHA) emergency response planning guideline (ERPG-2), the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms which could impair an individual's ability to take protective action is 50 ppm (0.0050%). The Scientific Committee on Occupational Exposure Limits (SCOEL) concluded that an occupational exposure limit (OEL) of 0.0001% (1.4 mg/m^3) for Hydrogen Peroxide, as 8-h time-weight average (TWA), is recommended [31]. NICNAS conducted a Tier II assessment on Hydrogen Peroxide under IMAP (see Non-Cosmetic Use section for more related information) [32]. It is advised that industries should use measures to minimize the risk of oral, dermal, ocular, and inhalation exposure to Hydrogen Peroxide by workers.

3. DISCUSSION

The study by William et al shows the mucolytic effect of the H_2O_2 which is increased by 250-fold in addition of ascorbic acid. This is supported by the findings of Pillai et al showing the mucolysis in peritoneal mucin. Table 1 shows the published safe concentrations of the hydrogen peroxide administered through inhalation and other modes in various animal and human studies.
On observing the inhalation effects of the H_2O_2, it is observed that up to 90% aqueous aerosol exposure of 107mg/m^3 administered in frequencies in mice for 2 weeks produces oedematous, nasal discharge and skin irritation. 50%aqueous concentration of 14.6mg/m^3 in rats for a period of 28 days produced irregular breathing and redness in nose. 1-6% aerosolized concentration administered in rabbits produced supersaturation of atria with oxygen and at concentrations of 30mg/m^3 in black rabbits, bleaching of fur and irritation of nose were reported. On human studies, 30% aqueous concentration of 3.08mg/m^3 increased nasal airway resistance was reported.
Table 1: safe concentrations of hydrogen peroxide in animal and human studies.

Figure 1: Concentration of Hydrogen Peroxide in mg/m3 vs Physiological Effect

S.NO.	PUBLISHED CONCENTRATION	EFFECTS
1.	0.2-3% in Peritoneal mucin	Mucolytic effect
2.	90% aqueous 107mg/m^3 in mice for 2 weeks	Oedematous feet, nasal discharge and skin irritation
3.	50% aqueous 14.6mg/m^3 in rats for 28 days	Irregular breathing, reddened nose.
4.	1-6% aerosolized in anesthetized rabbits	Supersaturation of atria with oxygen
5.	90% aqueous 30mg/m^3 in black rabbits	Bleaching of fur and irritation of nose.
6.	30% aqueous 3.08mg/m^3 to 10mg/m^3 in humans	Increase in Nasal Airway resistance

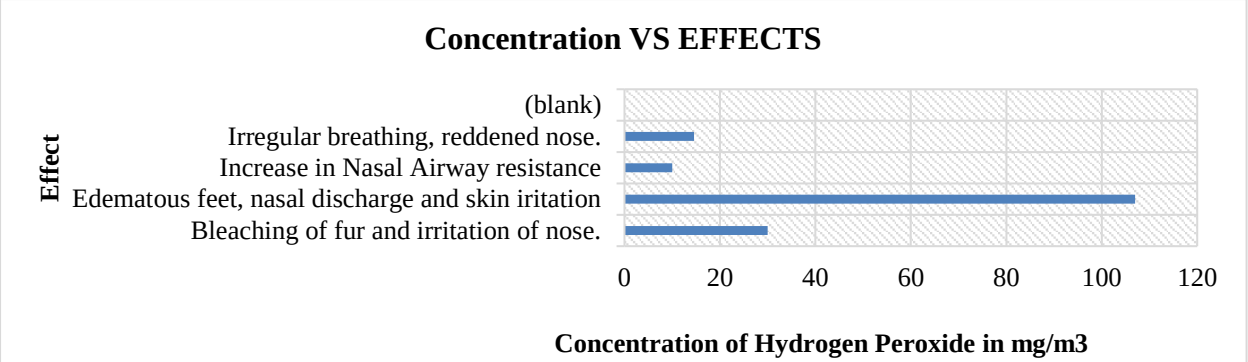

Table 2: conversion table for making various concentrations of H_2O_2

Quantity of Hydrogen Peroxide	*Quantity of water*	*% concentration of H_2O_2*
1 part 6% H2O2	1 part	3
	2 parts	2
	3 parts	1.5
	4 parts	1.2
	5 parts	1

The Study noted the issue of incidental inhalation exposure in aerosol hair sprays is about 4%. The available inhalation data suggest little potential for respiratory effects at relevant doses.

It should also be highlighted that inhalation toxicity studies on test animals are often conducted using high concentrations of droplets/particles with size distributions well within the respirable range and long exposure durations to ensure that the potential for pulmonary or systemic toxicity will be detected. In contrast, however, the concentrations of respirable droplets/particles and the inhalation exposure durations from the use of cosmetic products will be much less than those of the animal studies. A randomized, double-blind, parallel, placebo-controlled clinical trial by Di Domenico MB et al to assess the effectiveness of (1.0 %) gargling and (0.5%) nasal wash with H_2O_2 shows that H_2O_2 as a mouthwash and nasal spray is safe to use [37].

4. CONCLUSION

Thus, with the available toxicological data and safety reports, we can suggest that, a single exposure of 0.3% H_2O_2 in the external nostrils as a nasal wash with a subsequent blowing of nose can be helpful in decongestion and also in maintaining a sterile environment in the external nostrils. Still further studies are still required to provide accurate efficacy of the formulations developed.

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