Effect of distribution and membrane structure of alkalized lidocaine across an endotracheal tube cuff

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Lidocaine hydrochloride and alkalized lidocaine hydrochloride solutions were filled in endotracheal tube cuffs to determine the rate of diffusion of lidocaine across the cuffs, and assess the usefulness of these cuffs as a drug delivery system. Mallinckrodt™ Oral RAE® tracheal tubes were filled with three different lidocaine solutions, i.e., mixtures of 4% lidocaine hydrochloride solution and distilled water, 4% lidocaine hydrochloride solution and 8.4% sodium bicarbonate solution (LSB-Gr), and 4% lidocaine hydrochloride solution and dipotassium phosphate solution (LDP-Gr). Cuffs filled with the relevant lidocaine solution were placed in beakers filled with distilled water. A 100 μL sample of the water in the vessel was taken from each beaker every 30 minutes for 360 minutes to determine the concentration of lidocaine diffused across the cuff using fluorescence polarization immunoassay.

The cuff surface was observed after 60, 180, and 360 minutes of exposure for changes in the structure of the material. Lidocaine in LSB-Gr and LDP-Gr diffused across the cuffs at 30 minutes of exposure and thereafter. The lidocaine concentration in water in the vessel was 133.8 μg/mL for LSB-Gr, and 119.0 μg/mL for LDP-Gr. Although the cuffs did not rupture during exposure, the cuff material deteriorated over time. The results indicate that alkalization of intracuff lidocaine increases the rate of diffusion of lidocaine across the endotracheal tube cuff and affects the cuff material, which increases the risk of complications due to cuff rupture. (J Osaka Dent Univ 2016; 50: 1–6)

Key words : Lidocaine ; Alkalinization ; Endotracheal tube cuff ; Drug delivery system

INTRODUCTION

In order to prevent pharyngolaryngeal pain, the cough reflex and discomfort caused by use of an endotracheal tube during general anesthesia or after tracheotomy, endotracheal tube cuffs are filled with lidocaine solutions to maintain cuff pressure and provide surface anesthesia. Endotracheal tube cuffs have been reported useful as a drug delivery system. However, cuff rupture may occur and cause intoxication with the local anesthetic agent and mucosal damage. It has been reported that the rate of diffusion of lidocaine across endotracheal tube cuffs increases when lidocaine solution is warmed or alkalized with sodium bicarbonate. However, the effect of exposure to lidocaine or alkalized lidocaine solution on the risk of cuff damage is still unknown.

We alkalized 4% lidocaine hydrochloride solution with sodium bicarbonate solution (Meylon Injection 8.4%; Otsuka Pharmaceutical, Tokyo, Japan) or dibasic potassium phosphate (Dipotassium Phosphate Corrective Injection; Otsuka Pharmaceutical), which are used clinically for the treatment of electrolyte imbalances. We determined the amount of lidocaine diffused across the endotracheal tube cuff over time to assess the usefulness of lidocaine-filled cuffs as a drug delivery system, and observed the effect of lidocaine and alkalized lidocaine solutions on the integ-
rity of the endotracheal tube and the cuff material.

MATERIALS AND METHODS

Polyvinyl chloride (PVC) endotracheal tube cuffs with an internal diameter of 5.5 mm (Mallinckrodt™ Oral RAE® Tracheal Tube; Medtronic, Tokyo, Japan) were filled with 6 mL of one of the three different lidocaine hydrochloride solutions prepared using 4% lidocaine hydrochloride solution (pH 6.0-7.0; Xylocaine® solution 4%; AstraZeneca, Osaka, Japan) diluted with sterile water (Otsuka Distilled Water; Otsuka Pharmaceutical), 8.4% sodium bicarbonate solution (pH 8.6; MEYLON® Injection 8.4%; Otsuka Pharmaceutical), and dipotassium sulfate (K₂HPO₄) solution (pH 8.8; Corrective Use Dipotassium Phosphate Solution; Otsuka Pharmaceutical). The three solutions consisted of (1) a mixture of 2 mL of 4% lidocaine hydrochloride and 4 mL of sterile water (L-G, n = 5); (2) a mixture of 2 mL of 4% lidocaine hydrochloride solution and 4 mL of 8.4% sodium bicarbonate solution (LSB-G, n = 5); and (3) a mixture of 2 mL of 4% lidocaine hydrochloride solution and 4 mL of dipotassium phosphate solution (LDP-G, n = 5).

Immediately after each tube cuff was filled with the relevant solution, it was placed into a beaker containing 100 mL of distilled water to completely immerse it. The water in the beaker was maintained at 37°C and continuously mixed using a magnetic stirrer at 100 rpm. A 100 μL sample of the water was obtained every 30 minutes for 360 minutes to determine the concentration of lidocaine diffused across the cuff using a fluorescent polarization immunoassay (EPIA) (TDX analyzer; Abbott, Osaka, Japan). Following the experiment, the tube cuffs were retrieved from the beakers. Each tube cuff was filled with 6 mL of air via the pilot balloon, and was pressed with fingers to confirm whether the cuffs could be broken with manual pressure. In a separate experiment, three endotracheal tube cuffs each were filled with one of the three lidocaine solutions, and were immersed in water under the same conditions as in the first experiment. The cuffs were retrieved from the water 60, 180 and 360 minutes later, and the appearance of the inner surface of the cuffs was observed under a stereomicroscope.

Statistical Analysis

Lidocaine concentration was expressed as the mean and standard error. Non-repeated measures analysis of variance (ANOVA) was used to compare the lidocaine concentration at a given time point and that at the next time point, and the Bonferroni multiple comparison test was used to compare the groups. Significance was set at 5%.

RESULTS

The pH values of L-G, LSB-G and LDP-G were 6.70 ± 0.12, 7.90 ± 0.15, and 7.85 ± 0.16, respectively. When L-G was used, lidocaine concentrations in water samples ranged between 0.06 ± 0.04 μg/mL and 1.05 ± 0.34 μg/mL. The increase in lidocaine concentration became significant at 270 minutes and thereafter, and reached a peak of 1.05 ± 0.34 μg/mL at 300 minutes. When LSB-G was used, lidocaine concentrations ranged between 12.0 ± 3.74 μg/mL and 133.8 ± 23.2 μg/mL. The increase in lidocaine concentration became significant at 120 minutes and thereafter, and reached a peak of 133.8 ± 23.2 μg/mL at 300 minutes. When LSP-G was used, the concentration ranged between 11.4 ± 2.41 and 119 ± 14.8 μg/mL, and the increase became significant at 120 minutes and thereafter, and reached a peak of 119 ±
14.8 μg/mL at 360 minutes. Although the lidocaine concentrations with LSB-Gr and LDP-Gr were significantly different from those with L-Gr, no differences in lidocaine concentration were observed between LSB-Gr and LDP-Gr (Fig. 1).

L-Gr filled in tube cuffs did not change its appearance for 360 minutes. On the other hand, LSB-Gr and LDP-Gr became clouded immediately after mixing the lidocaine hydrochloride solution and the relevant alkaline solution, and formed visible crystals. However, cloudiness and crystals disappeared in 120 minutes, and a decrease in content of solution due to diffusion of lidocaine was observed at 360 minutes of immersion. No tube cuffs ruptured during the immersion. After the 360-minute immersion, 3 of the 6 cuffs filled with LSB-Gr and 2 of the 6 cuffs filled with LDP-Gr ruptured when manual pressure was applied. None of the 6 cuffs filled with L-Gr ruptured. Stereomicroscopy at

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**Control cuff**

![Control cuff](image1)

**Fig. 2-1** Stereomicroscopic observation of the control cuff.

![Control cuff](image2)

**Fig. 2-2** Lidocaine hydrochloride and sterile water (L-GR). No significant changes were observed in the cuff surface exposed to non-alkalinized lidocaine solution for 360 minutes as compared with the control cuff.
Fig. 2-3  Lidocaine hydrochloride and 8.4% sodium bicarbonate (LSB-Gr). On the other hand, the entire cuff surface exposed to lidocaine solutions with sodium bicarbonate became irregular after 60 minutes of exposure, and rough after 360 minutes (1,000 X magnification) as compared with the control cuff.

Fig. 2-4  Lidocaine hydrochloride and dipotassium phosphate solution (LDP-Gr). Again, the entire cuff surface exposed to lidocaine solutions with dipotassium phosphate became irregular after 60 minutes of exposure, and rough after 360 minutes (1,000 X magnification) as compared with the control cuff.
1000 X magnification revealed that the inner surface of the cuff exposed to L-Gr showed no changes after 60, 180 or 360 minutes. On the other hand, although the surfaces exposed to LSB-Gr and LDP-Gr had no apparent pin holes, they became irregular by 60 minutes and rough by 360 minutes as compared with the control cuff surface (Fig. 2).

**DISCUSSION**

In order to avoid unfavorable complications after extubation, such as hemodynamic changes, restlessness, dysphonia and hoarseness, anesthesiologists have filled endotracheal tube cuffs with local anesthetic solutions rather than air. The diffusion of lidocaine through this drug delivery system, especially that using alkalinized lidocaine solutions, has been investigated with *in vitro* and *in vivo* studies.\(^9\)\(^{11}\) In many studies, sodium bicarbonate was used to alkalinize lidocaine solutions. In the present study, 2 mL of 4% lidocaine hydrochloride solution was mixed with 4 mL of either 8.4% sodium bicarbonate solution or dipotasium phosphate corrective injection. The two alkalinized lidocaine solutions did not differ significantly in pH (7.90 ± 0.15 vs. 7.85 ± 0.16), and the amount of lidocaine that diffused across the cuff was similar. These results indicate that the rate of lidocaine diffusion depends upon pH rather than the type of the substance. It has been reported that when endotracheal tube cuffs are filled with lidocaine solutions alkalinized with sodium bicarbonate, the lidocaine concentration in the surrounding environment starts increasing at 45-65 minutes of exposure.\(^9\)\(^{11}\)

In this study, both sodium bicarbonate and dibasic potassium phosphate caused cloudiness and crystal formation immediately after being mixed with lidocaine solution. These solutions became clear after 90-120 minutes, and the concentration of lidocaine in the surrounding water increased as the amount of crystal decreased. These findings indicate that it takes considerable time to produce the neutral base form of alkalinized lidocaine at pH 7.85-7.90. As the ratio of ionized and nonionized species is a function of the pH of the substance and the pH of the dissolving medium (the Henderson-Hasselbalch equation), it is believed that the addition of sodium bicarbonate to alkalinize lidocaine solutions induces a permeation phenomenon.\(^10\)

In the present study, the concentration of lidocaine that diffused across the cuff started increasing after 120 minutes of immersion, and reached a peak of 120-130 μg/mL at 360 minutes when sodium bicarbonate or dipotassium phosphate was used to alkalinize the lidocaine solution. However, the lidocaine concentration in the surrounding water remained low during the first 90 minutes of immersion. These findings suggest that endotracheal tube cuffs filled with alkalinized lidocaine solutions may not be a useful drug delivery system for patients undergoing surgery with short-term intubation.

Estebe *et al.* have reported that when endotracheal tube cuffs are filled with a non-alkalinized lidocaine solution, only 1% of the lidocaine in the cuffs is distributed across the cuff. This result indicates that the solution in the cuff must contain 200-400 mg of lidocaine to obtain noticeable clinical effect, and the risk of cuff rupture is high. On the other hand, when alkalinized lidocaine solutions are used, the diffusion of 65% of the neutral base form of lidocaine hydrochloride through the hydrophobic structure of the polyvinyl chloride cuff within a 6-hour period showed that the use of a small dose (40 mg) of alkalinized lidocaine hydrochloride markedly improved endotracheal tube tolerance. They also suggested that the amount of lidocaine filled in the cuff may be decreased when the lidocaine solution is alkalinized.\(^9\)\(^{11}\)

However, once cuff damage occurs, serious complications such as intoxication with the local anesthetic agent and mucosal damage may develop. There have been no reports of cuff rupture associated with the use of lidocaine or alkalinized lidocaine solutions. No research has investigated the effect of these solutions on the cuff material. The effect of lidocaine on cuff material is still unclear. One report noted that although the use of lidocaine spray resulted in the formation of pin holes in the cuff, lidocaine solutions did not cause such change.\(^2\) Careful observation of appearance is important to assess the effect of lidocaine on polyvinyl chloride (PVC) cuffs. Scanning electron microscopy using an electron beam with a short wavelength is essential to observe changes in the cuff material.
material in a three-dimensional manner. In this experiment, no pin holes were observed in any cuffs exposed to the solutions. Lidocaine diffused across the cuff over time, and the cuff material did not swell during the immersion period.

However, our results indicated that manual pressure may cause cuff rupture when cuffs are exposed to alkalinized lidocaine solutions for 360 minutes. Stereoscopic microscopy of the inner surface of the cuffs revealed that although the cuff material was not influenced by the non-alkalinized lidocaine solution, it was altered by the exposure to the alkalinized lidocaine solutions. The entire surface became irregular after 180 minutes of exposure, and the material deteriorated and became fragile after 360 minutes of exposure. Many endotracheal tubes including infusion tubes and cuffs are made of PVC, and are resistant to alkaline solutions. These products often contain di(2-ethylhexl) phthalate (DEHP) as a plasticizer agent, and highly liposoluble drugs may enhance the dissolution of DEHP from PVC products, which may negatively affect the human body. It is unknown whether lidocaine enhances the dissolution of DEHP from PVC. However, the use of endotracheal tube cuffs filled with alkalinized lidocaine solutions may pose a risk to the human body, as our results indicate that alkalinized lidocaine solutions affect the surface structure of endotracheal tube cuffs.

In conclusion, endotracheal tube cuffs filled with alkalinized lidocaine solutions, which distribute lidocaine across the cuff after 120 minutes of exposure and thereafter, are considered beneficial as a drug delivery system that prevents postoperative complications associated with intubation and extubation. However, the cuffs must be treated with care because cuffs filled with alkalinized lidocaine solutions may be damaged by compression during an operation.

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REFERENCES