



Original article

In vitro evaluation of diffusion of lidocaine and alkalized lidocaine through the polyurethane membrane of the endotracheal tube



Évaluation in vitro de la diffusion de la lidocaïne-bicarbonatée au travers des ballonnets en polyuréthane des sondes d'intubation

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ABSTRACT

Objectives. – Endotracheal tube (ETT) and its inflated cuff are likely to induce specific reactivity at the emergence time. In ICU, the tolerance of the ETT cuff could be a part of patient agitation and increased of sedation.

Materials and methods. – Using specific ICU ETT cuff (thin polyurethane cuff), we perform an *in vitro* evaluation of diffusion of lidocaine and alkalized lidocaine (L-B) across the PU cuff for a long duration. We evaluate the safety of this procedure by a daily injection into the cuff.

Results. – With lidocaine alone, we observed a low rate of diffusion through the cuff (< 8% over 24 h), whereas the L-B solution had a high diffusion (> 90% over 24 h). The released profiles were similar from day 0 to day 8, and no cuff rupture was reported over the 8-day study.

Conclusion. – The safety, controlled release, and lack of deleterious effects on cuff membrane were confirmed. In case of unexpected cuff rupture, an adequate determination of the mixture allows to obtain a safe solution with the achievement of a physiological pH (7.4) and the small dose of lidocaine (40 mg).

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R É S U M É

Objectifs. – Les ballonnets des sondes d'intubation sont responsables de phénomènes d'irritation voire d'intolérance trachéale lors de la récupération de la conscience. En réanimation, ces phénomènes peuvent être en partie responsable de l'agitation des patients et peuvent nécessiter une sédation elle-même responsable d'une prolongation d'hospitalisation. De nouveaux ballonnets en polyuréthane aux parois très fines ont pour but d'améliorer cette tolérance trachéale. Le but de l'étude a été d'évaluer *in vitro* la diffusion de la lidocaïne-bicarbonatée (L-B) au travers des parois fines de ces ballonnets durant une période prolongée.

Matériels et méthodes. – Comme déjà décrit avec le PVC de ballonnets d'anesthésie (petit volume, haute pression), nous avons évalué, *in vitro*, les possibilités de diffusion de la lidocaïne (L) et de la L-B sur une période prolongée de 24 heures et répétée sur 8 jours.

Résultats. – La L seule diffuse très peu (moins de 8 % sur 24 heures) alors que la L-B diffuse à 90 % sur 24 heures. Avec un remplissage quotidien durant 8 jours, nous n'avons pas trouvé de différence dans les profils de diffusion et nous n'avons rapporté aucune fuite. L'utilisation répétée de la L-B dans le remplissage de ballonnets à très fines parois (7 m d'épaisseur) ne semble pas être toxique.

Conclusion. – Des études cliniques semblent donc possible, ce d'autant qu'à l'inverse de la L seule, le pH de la solution L-B a été contrôlé à 7,4 et que la dose totale de L ne dépassant pas les 40 mg, ce qui serait sans danger en cas de rupture.

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1. Introduction

Airway management has always been a major worry for anesthesiologists. For many years, the intubation was considered as the most critical period. However, the extubation is also a critical situation. Endotracheal tube (ETT) and its inflated cuff are likely to induce specific reactivity at the emergence time: cough, sore throat, and dysphonia due to mucosal injury (ciliary loss, inflammation, ulceration, and hemorrhage), but also laryngospasm, tachycardia, hypertension, cardiac ischemia, bleeding, and increased intracranial and intraocular pressures. In addition, patients may move and be exposed to accidental self-extubation without any cuff deflation, which can lead to vocal cords injuries. The occurrence of some of these adverse effects ranges from 40 to 90% [1–4]. Potential causes for the phenomena that occur at the emergence time are mostly related to mechanical irritation due to the ETT: inflation and/or over-inflation of the ETT cuff, positive pressure ventilation of the lungs, chemical irritation caused by inhaled agents and oxygen, and subglottic secretions that accumulated above the ETT cuff.

Strategies to decrease these potential causes of airway irritation at the extubation time were evaluated in anesthesia. Non-pharmacological methods were evaluated: smaller-sized ETT, lubricating the ETT, intubation after full muscle relaxation, gentle oropharyngeal suctioning, control of the pressure cuff, and extubation under deep anesthesia [5–7]. Pharmacological procedures were also proposed as beclomethasone inhalation, gargling with mixture of azulene sulfonate-aspirin-benzylamine hydrochloride or licorice, lidocaine intravenous, narcotics administration, lubrication of fluticasone, and lidocaine spray [8–10]. However, number of these procedures can only be used for a relative short duration of tracheal intubation.

The recent review performed by the *Cochrane Database* [11] established the effectiveness of topical and systemic lidocaine for the prevention of postoperative sore throat consecutive to intubation. However, probably due to the low pH of the lidocaine (i.e. lidocaine hydrochloride) commercially available, the use of lidocaine spray or jelly applied on tracheal mucosa or on the ETT increased the risk of sore throat [5–7,10].

Compared to air filling, some authors reported that lidocaine given into the cuff seems to be effective to reduce postoperative sore throat after extubation [12–17]. However, we had previously shown [18] that the lack of diffusion of lidocaine through the membrane of the ETT cuff might explain the lack of effect reported in the literature when the ETT cuff was inflated with lidocaine alone compared to saline [19,20]. Due to a very low rate of diffusion of lidocaine hydrochloride through the hydrophobic membrane (< 1%) [18], only the hydrophobic neutral form of lidocaine as a base is able to diffuse through the membrane of the ETT cuff. So the diffusion of lidocaine might be increased if combined with bicarbonate [21]. Clinical trials confirmed decreased sore throat and hoarseness after filling the cuff with a mixture of lidocaine-bicarbonate (L-B) compared to air or lidocaine filling [21–23]. This is particularly true for smoker patients [24,25]. Filling the ETT cuff with buffered lidocaine seemed to be more effective than lidocaine used through the Laryngotracheal Instillation of Topical Anesthesia (LITA) [26]. This good diffusion of lidocaine as L-B mixture allowed to use only a very small dose of lidocaine (40 mg) instead of the previously given large amount when lidocaine was used alone (200 to 500 mg) [16,17]. In case of rupture of the cuff, these latter amounts might be more dangerous by pulmonary vascular uptake and more irritant due to the pH than small lidocaine dose.

In the aim to allow a prolonged intubation, instead of ETT anesthesia cuff (i.e. polyvinylchloride: PVC, low-volume and high-pressure: LVHP), specific designs for endotracheal cuff were developed: high-volume and low-pressure (HVLP) cuff or polyurethane cuff (thickness 7 μm instead of $\geq 50 \mu\text{m}$). Diffusion of

L-B mixture has never been evaluated experimentally or clinically for these ETT cuffs. This is the reason why, before performing any clinical trial, we designed an experimental study to answer the following questions:

- what is the diffusion of lidocaine and L-B mixture across the polyurethane ETT cuff?
- what is the lidocaine profile of release for a long duration (more than 4 to 6 h usually published) and what is the profile of release in case of new administration into the cuff?

2. Material and methods

Polyurethane cuff ETTs (supplied by Kimberly Clarke Corp, Roswell USA) were inflated using different bicarbonate concentrations in lidocaine solution. Release of lidocaine from ETT cuffs was measured using a dissolution system [18,22]. Briefly, lidocaine hydrochloride was obtained from Astra-Zeneca Corp (AstraZeneca, Rueil Malmaison, France) and bicarbonate was supplied by B. Braun Medical S.A. (sodium bicarbonate, Boulogne, France).

Release of lidocaine from ETT cuffs was measured using a Distek dissolution test system Model 5100 A (Distek, North Brunswick, NJ, USA). It consisted of six independent cylindrical flasks with spherical bottoms, each containing 900 mL release medium, and a rotating paddle apparatus operating at 100 rpm, providing United State Pharmacopeia official method of dissolution. Sets of polyurethane ETT were immersed in release medium consisting of pH 7.4, 0.05 M phosphate buffer thermostated at 37 °C. For each set, one of the following solutions with 8 mL final volume was placed inside the ETT cuffs. The lidocaine concentration was measured continuously at 205-nm every 15 min for a 24 h period using a Specord 205 model spectrophotometer (AnalytikJena Instruments, Jena, Germany). All ETT were tested only once.

In the aim to obtain a pH of L-B mixture around 7.4, we evaluate the pH of various concentrations of lidocaine (1% to 10%) with digital pH meter. Then, with various concentrations of bicarbonate (1.4 to 8.4%), we determined the required volume to obtain pH of 7.4 with 1% of lidocaine.

In second step, we compared the release of lidocaine after cuff inflation with 40 mg of 1% lidocaine with ($n=3$) or without bicarbonate ($n=6$). Serum saline was added as requested in the aim to obtain 8 mL final volume. A dose ranging study with various volumes of 1.4% bicarbonate ($n=3$) was performed. Using the same ETT, we compared the release profile at day 0 to day 3 and at day 8, with the cuff emptied and refilled with the same concentration solution (4 mL of 1% lidocaine plus 4 mL of 1.4% of bicarbonate) every 24 h or 120 h (see Table 1).

Statistical analysis: data are expressed as mean \pm standard deviation (SD). The release profile of lidocaine in the suspension medium was plotted over time and graphically displayed and summarized for each set of experiments as group means. To compare lidocaine release profile, we used a model-independent method [27]. The similarity factor has been adopted by the Center for Drug Evaluation and Research (FDA) and by Human Medicines Evaluation Unit of the European Agency for the Evaluation of Medicinal Products (EMA), as a criterion for the assessment of the similarity between two *in vitro* dissolution profiles. The pairwise procedure includes the difference factor and the similarity factor.

The difference factor (f_1) measures the percent error between two curves over all time points:

$$f_1 = \frac{\sum_{t=1}^n (R_t - T_t)}{\sum_{t=1}^n R_t} \times 100$$

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