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Evaluation of systemic exposure to ipratropium bromide delivered by mesh type nebulizer during general anesthesia

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Ipratropium Bromide

The active ingredient in ATROVENT HFA Inhalation Aerosol is ipratropium bromide. It is an anticholinergic bronchodilator which appears to inhibit vagally-mediated reflexes by antagonizing the action of acetylcholine, the transmitter agent released at the neuromuscular junctions in the lung. Anticholinergics prevent the increases in intracellular concentration of cyclic guanosine monophosphate (cyclic GMP) which are caused by interaction of acetylcholine with the muscarinic receptors on bronchial smooth muscle [1].

Nebulizer

In medicine, a nebulizer is a drug delivery device used to administer medication in the form of a mist inhaled into the lungs. Nebulizers are commonly used for the treatment of cystic fibrosis, asthma, chronic obstructive pulmonary disease and other respiratory diseases [2].

1. Types of nebulizer

1) Jet nebulizer

The most commonly used nebulizers are Jet nebulizers, which are also called "atomizers". Jet nebulizers are connected by tubing to a compressor that causes compressed air or oxygen to flow at high velocity through a liquid medicine to turn it into an aerosol, which is then inhaled by the patient. Currently there seems to be a tendency among physicians to prefer prescription of a pressurized Metered Dose Inhaler (pMDI) for their patients, instead of a Jet nebulizer that generates a lot more noise (often 60 dB during use) and is less portable due to a heavier weight. However Jet nebulizers are commonly used for patients in hospitals who have difficulty using inhalers, such as in serious cases of respiratory disease, or severe asthma attacks. The main advantage of the Jet nebulizer is related to its low operational cost. If the patient needs to inhale medicine on a daily basis the use of a pMDI can be rather expensive. Today several manufacturers have also managed to lower the weight of the Jet nebulizer down to 635 grams, and thereby started to label it as a portable device. Compared to all the competing inhalers and nebulizers, the noise and heavy weight is however still the biggest drawback of the Jet nebulizer.

2) Vibrating mesh nebulizer

A new significant innovation was made in the nebulizer market around 2005, with creation of the ultrasonic Vibrating Mesh Technology (VMT). With this technology a mesh/membrane with 1000－7000 laser drilled holes vibrates at the top of the liquid reservoir, and thereby pressures out a mist of very fine droplets through the holes. This technology is more efficient than having a vibrating piezoelectric element at the bottom of the liquid reservoir, and thereby shorter treatment times are also achieved. The old problems found with the ultrasonic wave nebulizer, having too much liquid waste and undesired heating of the medical liquid, have also been solved by the new Vibrating Mesh nebulizers. A partial list of available VMT nebulizers includes: Pari eFlow, Respironics i-Neb, Omron MicroAir, Beurer Nebulizer IH50, and Aerogen Aeroneb. As the price of the ultrasonic VMT nebulizers carry a higher price compared to the previous models, most of the manufacturers continue also to sell the more "old fashioned" Jet nebulizer.

2. Comparison of nebulizers on pulmonary drug delivery

The jet type (Pariboy SX, PARI. Co. Ltd, Germany) and mesh type (NE-SM1, KTMED Co. Ltd, Korea) nebulizers were tested to evaluate efficacy of pulmonary drug delivery in surgical patients during mechanical ventilation. A total of 20 patients was

Table 1. Noncompartmental Pharmacokinetic Parameters after Administration of 500 μg Ipratropium Bromide using Jet or Mesh Type Nebulizer

Nebulizer	Dose-normalized C_{max} (pg/ml)	Dose-normalized AUC_{last} (min·pg/ml)	Dose-normalized AUC_{inf} (min·pg/ml)
Jet type (n=10)	1.0 ± 0.4	105.6 ± 33.3	166.6 ± 51.9
Mesh type (n=10)	0.6 ± 0.2	105.3 ± 23.7	168.2 ± 101.3

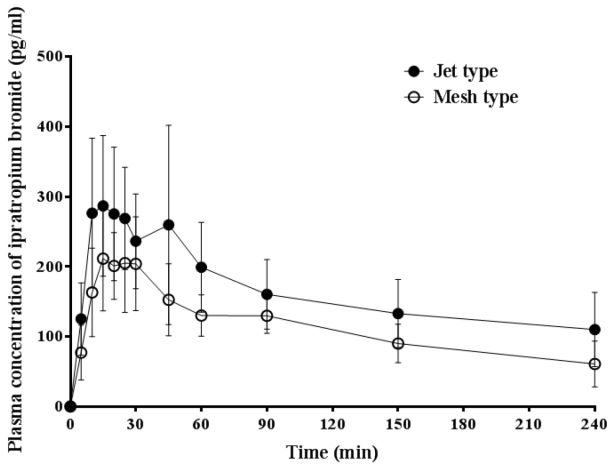

Fig. 1. Mean plasma concentration over time after administration 500 μg ipratropium bromide using jet or mesh type nebulizers.

randomly allocated with two groups. Ipratropium bromide of 500 μg was placed in the reservoir of each nebulizer. All of the nebulizers were run continuously until they no longer produced aerosol. The ventilator settings were V_T 8 ml/kg, respiratory rate 10 breaths/min and inspiratory pause 50%. During the drug administration, arterial blood samples (10 ml) were obtained at preset intervals: 0, 5, 10, 15, 20, 25, 30, 45, 60, 90, 150, 240 min after the start of ipratropium administration [3]. The dose-normalized AUC_{last} and AUC_{inf} (area under the curve from administration to the last measured concentration and to infinite, respectively) were calculated using WinNonlin 6.3 (Certara, St. Louis, MO, USA).

Results

Pharmacokinetic parameters including dose-normalized C_{max}, AUC_{last} and AUC_{inf} did not significant differences between both groups.

The jet type nebulizer generated a lot more noise and had an incorrect influence on respiratory monitoring.

Conclusion

The mesh type nebulizer showed similar performance on pulmonary drug delivery in surgical patients during mechanical ventilation, compared with jet type nebulizer. Also, mesh type has absolutely no noises at all and does not influence on respiratory monitoring during mechanical ventilation.

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Use of bioimpedance spectroscopy for assessing body water composition in healthy volunteers receiving various types of fluid

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There have been a ongoing research regarding the method of intravenous fluid administration to maintain perfusion pressure in vital organ without excessive fluid accumulation. Traditionally, the infusion of crystalloid enough to maintain an adequate renal perfusion pressure has been considered as an acceptable fluid administration technique [1]. This infusion modality is also called as liberal replacement. However, some reports have shown that liberal replacement is associated with an increased incidence of postoperative morbidities and longer hospital admission compared to restrictive replacement in which colloid instead of crystalloid is mainly infused intraoperatively [2]. Most studies have evaluated which fluid types is suitable during intraoperative periods by comparing clinical outcomes depending on the types of fluid since it is quite difficult to evaluate the redistribution of fluid between compartments in quantitative way.

It is possible to evaluate the redistribution of fluid volume between compartments quantitatively with dye indicator. However, it takes a longer time, and is expensive and invasive technique in nature [3]. Clinically, we usually evaluate the extent of fluid redistribution as weight gain after fluid administration indirectly. However, the limitation of evaluation fluid redistribution as weight gain is that weight gain is not the direct outcome during fluid redistribution, but after fluid administration. If we have an information of the exact time course of fluid redistribution after administration depending on fluids types, we can easily determine the volume and rate of administered fluid to maintain an adequate intravascular volume. Also, if we can make an index of the extent of fluid redistribution and fluid volume non-invasively, this non-invasive method can replace an traditional method of quantifying the redistribution of body fluid invasively.

Bioelectrical impedance spectroscopy (BIS) is a recently developed method to quantify body fluid volume in different body compartments based on the electrochemical conductance of tissue is different depending on body tissue [4]. Fluid determination via bioelectrical impedance methods is easy to perform, non-invasive, rapid and allows repeated measurements with excellent inter-observer reproducibility. Bioimpedence spectroscopy provides a predictor of fluid overload in peritoneal dialysis patients [5].

Therefore, we aimed to perform a clinical trial to evaluate the changes in intracelluar water, extracelluar water, and their ratio, measured by bioempedance spectroscopy, in response to the volume of hypotonic crystalloid, isotonic crystalloid and colloid infused in healthy volunteers.

This study was performed in randomized, crossover design. In random sequence, the adult volunteer received Hartman solution, volulyte® (6% hydroxyethyl starch 130/0.4, Fresenius Kabi AG, Bad Homberg, Germany), 5% Dextrose solution, respectively. The infusion interval was set at the least 7 days. 4 ml/kg of Hartman solution was administered at 10 times, which was set at least 2 min. After bolus administration, fluid volume at intracellular and extracellular compartment was measured by indocyanine green (ICG), BIS, respectively. The intracellular, extracellular fluid volume, and its ratio was calculated by indocyanine green (ICG), BIS, respectively 5, 10, 15, 20, 30, 40, 60, 90, 120, 180, 240, 360, 480 min after the last bolus administration. 2 ml of 5% Dextrose solution was administered at 10 times, which was set at least 2 min. After bolus administration, fluid volume at intracellular and extracellular compartment was measures by indocyanine green (ICG), BIS, respectively. The intracellular, extracellular fluid volume, and its ratio was also calculated by indocyanine green (ICG), BIS, respectively 5, 10, 15, 20, 30, 40, 60, 90, 120, 180, 240, 360, 480 min after the last bolus administration. 100 ml of Volulyte® was administered at 10 times, which was set at least 2 min. After bolus administration, fluid volume at intracellular and extracellular compartment was measures by indocyanine green (ICG), BIS respectively. The intracellular, extracellular fluid volume, and its ratio was calculated by indocyanine green (ICG), BIS, respectively 5, 10, 15, 20, 30, 40, 60, 90, 120, 180, 240, 360, 480 min after the last bolus administration. NONMEM software allowed us to model the redistribution of

crystalloids and colloid quantitatively with the use of intracellular, extracellular fluid volume calculated by ICG, BIS respectively

In this session, we briefly introduce the experience to quantify the fluid volume with BIS in adult volunteer receiving hypotonic crystalloid, isotonic crystalloid and colloid and suggest clinical applicability of BIS as an indicator of fluid therapy.

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