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Inhalational therapy during mechanical ventilation

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Introduction

The pulmonary route as a method of drug delivery is readily accessible during mechanical ventilation (MV). Nitric oxide, perfluorocarbon, prostacyclin, surfactant, antibiotics and bronchodilators have been administered by this route. In general, the airway is preferred to the intravenous route because all of these pharmacological agents are directly applied to the target organ. Consequently, adequate concentrations can be achieved in the lung to produce a therapeutic effect without concentrations in other organs that may cause toxic side effects.

Traditionally, small-volume nebulizers (consisting of a disposable or reusable nebulizer and a pressurized gas source) have been used for bronchodilator inhalation during MV. Recently, several investigators have reported that administration of bronchodilators with metered-dose inhalers (containing medications in suspension or solution, a metering valve and a propellant) are also effective. These reports, combined with several disadvantages of small volume nebulizers (increased cost, risk of contamination, personnel time, decreased reliability), favored the use of metered-dose inhalers (MDI) during MV.

Theoretically, many variables may influence aerosol deposition during MV. Several authors have studied aspects of drug administration and delivery in an attempt to find the optimal technique of administration of MDIs. Dhand et al. have previously reviewed this topic (Dhand R et al. 1996 *Eur Respir J* 9:585–595 and 1997 *Am J Respir Crit Care Med* 156:3–10). I will discuss the most recent data dealing with the several unresolved aspects of inhalational therapy during MV.

Mouloudi E, Katsanoulas K, Anastasaki M, Askitopoulou E, Georgopoulos D (1998) Bronchodilator delivery by metered-dose inhaler in mechanically ventilated COPD patients: influence of end-inspiratory pause. *Eur Respir J* 12: 165–169

The authors examined the effects of bronchodilator delivery by MDIs and observed the influence of an end-inspiratory pause on the measured baseline airway pressures and mechanics of the respiratory system in 12 patients mechanically ventilated for acute exacerbations of chronic obstructive pulmonary disease (COPD). In a prospective, randomized manner they administered six puffs of salbutamol (via a cloud spacer inserted in the inspiratory limb of the ventilator circuit) to these patients during volume controlled ventilation, with and without a 5-s end-inspiratory pause. Each patient served as his/her own control after a 6-h wash-out period. In both groups, after 15 min of salbutamol, static and dynamic airway pressures, auto-positive end-expiratory pressure (auto-PEEP), maximum, and minimum airflow resistances and the difference between the last two parameters decreased. These data confirmed that use of β -agonists via an MDI decreased inspiratory and expiratory resistance in mechanically ventilated patients with acute exacerbations of COPD and that application of a 5-s end-inspiratory pause did not influence the therapeutic effect.

Wildhaber JH, Hayden MJ, Dore ND, Devadson SG, LeSuef PN (1998) Salbutamol delivery from a hydrofluoroalkane pressurized metered-dose inhaler in pediatric ventilator circuits. An in vitro study. Chest 113: 186–191

In this in vitro study (a ventilated lung model with a pediatric circuit) the investigators aimed to determine the efficacy of salbutamol delivery from a hydrofluoroalkane (as a propellant) pressurized MDI. The results demonstrated that salbutamol delivery with hydrofluoroalkane is similar to the reported albuterol delivery from a chlorofluorocarbon-containing MDI from a previous study. This study then determined the effect of electrostatic charge on salbutamol delivery with an MDI using an in-line small or large chamber device. They showed that reducing the electrostatic charge increased the delivery of small particles ($< 3.1 \mu\text{m}$) from the small and large in-line holding chambers. An electrostatic charge did not affect delivery from a non-chamber device. Finally the authors assessed the effects of various ventilator settings on salbutamol delivery by MDI in four different models. The models simulated different weights of children, and used either an in-line non-chamber or a small or large chamber device (coated with an ionic detergent to reduce the electrostatic charge). Results suggested that, when placed between the Y connector and the endotracheal tube during ventilation with low tidal volume, holding chambers are more efficient than in-line non-chamber devices. The large chamber had no advantage over the small chamber. Changing the compliance of the lung model without changing the ventilatory conditions did not alter drug delivery. However, a heated and humidified ventilator circuit decreased drug delivery compared to dry conditions.

Torres A, Anders M, Anderson P, Heulitt JM (1997) Efficacy of metered-dose inhaler administration of albuterol in intubated infants. Chest 112: 484–490

In this study, the authors compared the efficacy of MDI delivery with nebulizer delivery of albuterol in 11 mechanically ventilated pediatric patients. After a trial of albuterol by a nebulizer system, the infants with bronchiolitis found to respond to this bronchodilator were included in the study. Albuterol was then delivered by MDI and nebulizer devices in a randomized manner. Each patient served as his or her own control. Both methods of administration were associated with a similar improvement in pulmonary function as measured by respiratory system resistance and compliance. This study is the first clinical study in a mechanically ventilated pediatric population showing that both methods of albuterol administration are efficacious and safe.

Fok T, Al-Essa M, Monkman S, Dolovich M, Girard L, Coates G, Kirpalani H (1997) Pulmonary deposition of aerosol delivered by metered dose inhaler, jet nebulizer, and ultrasonic nebulizer in mechanically ventilated rabbits. Pediatr Res 42: 721–727

These authors compared the deposition efficiency of aerosolized salbutamol to the lungs of mechanically ventilated rabbits by MDI with either a holding chamber, jet nebulizer or an ultrasonic nebulizer with a large or small cup. To accomplish this comparison they labeled salbutamol aerosol with technetium-99 m and, after delivery with the four different devices, measured the radioactivity of the lungs, the trachea and the ventilator circuit. From these measurements they estimated total pulmonary salbutamol deposition as a percentage of total pulmonary drug delivery. Drug delivery to the lung was significantly higher with the small cup ultrasonic nebulizer. They concluded that the ultrasonic nebulizer with a small medication reservoir delivers a significantly greater amount of aerosol to the lungs of ventilated rabbits than other devices.

Discussion

According to the articles summarized, recently some insights have been gained into various aspects of the use of MDI in mechanically ventilated patients. From the accumulated data in the literature we already know that many variables can influence aerosol deposition. An optimal administration technique must be defined to obtain the desired response to bronchodilators in mechanically ventilated patients. According to these papers we may conclude:

1. MDIs can be used in the adult patient population during MV.
2. An end-inspiratory pause does not seem necessary in adult COPD patients during MV.
3. MDIs and jet nebulizers seem to be equally effective in pediatric patients during MV.
4. Large-volume chambers are not more efficient than small-volume chambers in the pediatric population.
5. Electrostatic charge and circuit humidification play an important role in aerosol delivery.
6. Ultrasonic nebulizers with a small volume cup may be the most efficient method of treating pediatric patients during MV with bronchodilator drugs.
7. Hydrofluoroalkane can be used as a propellant.

More data are needed, especially in pediatric patients. According to the studies of Fok et al., Torres et al. and Wildhaber et al., there are some indications that MDI and small-volume nebulizers are equally effective in the pediatric patients. However, Fok et al. also concluded

ed that in experimental settings an ultrasonic nebulizer with a small medication reservoir is superior to the other methods tested. Exact conclusions are difficult to draw because one of the studies was an in vitro study, one used rabbits and the last one was on pediatric patients. The authors have mentioned that their data cannot be fully extrapolated to the clinical setting.

There are also other questions that need to be answered. We need studies on the use of MDI with a nozzle extension. Are there some patients who will respond

to increasing doses with MDI during MV? What will be the influence of increasing the dose given by MDI on other factors affecting the deposition of bronchodilators in the lung? Do we need to monitor the effect of bronchodilators during and after their administration in mechanically ventilated patients? If yes, how shall we do it? Is there any place for dry powder inhalers during MV? What are the indications for using bronchodilators during MV? And finally, do they have any role in the acute respiratory distress syndrome?