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The efficiency of β_2-agonist delivery through tracheal tubes with the metered-dose inhaler: an in vitro study

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Abstract

Purpose. To study the delivery efficiency of procaterol aerosols administered through the tracheal tube (ETT) with a metered-dose inhaler (MDI) during apnea.

Methods. First, in a normal room air environment (at ambient temperatures of 24° to 26°C), we measured the amount of aerosol delivered through the ETT by comparing the weight of a 2-l bottle before and after firing the MDI directly into the 15-mm adapter of the ETT. The distal half of the ETT was inserted in the bottle. This procedure was repeated using five different ETTs with an internal diameter of 4–8.5 mm. The delivery efficiency was obtained by dividing the amount of aerosol delivered through the ETT by the total aerosol output per MDI puff. Next, we investigated whether the connector attached to the 15-mm ETT adapter could reduce the delivery, by repeating the same procedure with 4-mm and 5-mm ETTs. Finally, we compared the efficiencies of aerosol delivery through the 5-mm ETT and the 7.5-mm ETT in a normal room air environment with results obtained under a humidified condition (100% humid air at 37°C).

Results. The percentages of aerosol delivered through the ETTs in a normal room air environment were 40%–60%, except for the 4-mm ETT, for which the percentage was 32.7% ± 6.6% ($P < 0.05$ *vs* that with the 5-mm ETT or the 6-mm ETT). A connector attached to the 15-mm ETT adapter significantly decreased the delivery efficiencies (19.0% ± 5.8% *vs* 32.7% ± 6.6% with the 4-mm ETT, 24.6% ± 11.8% *vs* 51.7% ± 10.8% in the 5-mm ETT) when compared with those without a connector. The delivery efficiencies under the humidified condition in the 5-mm ETT and the 7.5-mm ETT were 65.5% ($P < 0.05$) and 89.8% of those in the normal room air environment, respectively.

Conclusion. The efficiency of delivery of procaterol aerosol through the ETTs was unexpectedly high (approximately half of the total aerosol output per MDI puff in the 5-mm to 8.5-mm ETTs, and one third of the total aerosol output per MDI puff in the 4-mm ETT). A connector attached to the 15-mm ETT adapter noticeably decreased the delivery efficiency. In the smaller-sized ETT, delivery efficiency was significantly lower under the humidified condition than in the normal room air environment.

Key words Metered-dose inhaler · β-Agonist · Tracheal tube · Bronchodilator · Bronchial asthma

Introduction

Inhalation of metered doses of β_2-adrenergic agonists is important and useful for the treatment of bronchial asthma. However, not more than about 15% of the inhaled β-agonist is delivered into the distal airways and the lungs. This is due to deposition in the oropharynx and large conducting airways when the aerosol is inhaled through a metered-dose inhaler (MDI) [1,2]. In a mechanically ventilated patient, the percentage of aerosol delivered to the small conducting airways and the lungs is 10% to 38% when the MDI is fired into the spacer placed between the patient Y connector and the inspiratory limb of the ventilator circuit [3–5]. (The low value of this range was obtained by measuring the deposition of radioactivity in the lungs [3] and the serum albuterol levels [4]. The high value was obtained by analysis of urinary albuterol levels [5].) The delivery decreases to less than 10% when the MDI is activated at the MDI actuator/adapter attached to the tracheal tube (ETT) [3,5]. However, actual clinical experience shows that β_2-agonists are effective in asthmatic attacks when the MDI is fired directly into the 15-mm ETT adapter. We therefore studied the efficiency of delivery of procaterol (a β_2-adrenergic agonist) aerosol through ETTs with five different internal diameters by an in vitro experiment using the MDI. Some of the devices mentioned in this article are explained in Table 1.

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Table 1. Brief explanation of the devices mentioned in this article

15-mm Tracheal tube (ETT) adapter: an adjunct of the ETT. It is also called a slip joint.
Connector: a part of the flexible connecting tube. It has a 15-mm female fitting and is 5 cm in length.
Metered-dose inhaler (MDI) actuator/adapter, elbow adapter with the MDI actuator, and swivel adapter: these adapters are L-shaped devices that adapt to the ETT and the patient Y connector and usually have side ports that allow actuation of the MDI along the same axis as the tracheal tube. They are alike except that the angles of these devices differ slightly from each other. The swivel adapter has two parts that can turn independently.
Spacer and reservoir: both of these are types of chamber devices and are usually equipped with the MDI actuator. They are used interchangeably.

Materials and methods

Materials

The following materials were used in this study.

Polyvinyl chloride ETTs with internal diameters of 4, 5, 6, 7.5, and 8.5 mm (Trakiron, Terumo, Tokyo, Japan), 20, 24, 28, 30.5, and 32.5 cm in length, respectively.
A 2-l plastic bottle.
A chlorofluorocarbon-propelled MDI of procaterol (Meptin, Otsuka Pharmaceutical, Tokushima, Japan).
An electronic scale with a reading accuracy of 1 mg (MC1 electronic scale LC1200S, Sartorius, Goettingen, Germany).
Connectors with a standard 15-mm female fitting, 5 cm in length (a part of the flexible connecting tube) (Kimura Medical, Tokyo, Japan).
A humidifier (Respiratory humidifier MR730, Fisher and Paykel Healthcare, Auckland, New Zealand).
A thermometer and hygrometer (Moiscope, Senko Medical, Tokyo, Japan).

Methods

A full MDI was fired four times into the air before the first experiment, because there was a possibility that the first or second activation of the MDI could deliver an unexpected amount of aerosol.

In the first experiment, the total aerosol output per MDI puff was obtained by weighing the MDI and reweighing it after a single puff. The purpose of this was to obtain a common total aerosol output per puff to calculate the percentage of aerosol delivered through ETTs in the second and third experiments. The MDI canister was shaken vigorously before actuation and was discharged in an inverted vertical position. This procedure was repeated five times in this experiment and five times again after the third experiment.

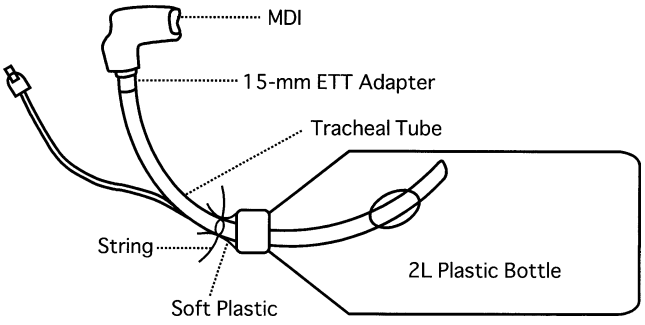

Fig. 1. Illustration of a laboratory setting for the measurement of the amount of procaterol aerosol delivered through the tracheal tube (*ETT*) from the metered-dose inhaler (*MDI*). The distal half of the ETT is inserted into a 2-l plastic bottle. The bottle is closed by tying a string around the soft plastic that wraps the ETT at the outlet of the bottle. The MDI is placed directly onto the 15-mm ETT adapter

In the second experiment, the distal half of the ETT was inserted into a 2-l plastic bottle. The bottle was closed by tying a string around a piece of soft plastic that was used to wrap the ETT at the outlet of the bottle. The MDI was then fired directly into the 15-mm ETT adapter (Fig. 1). The ETT was then pulled out of the bottle, and the bottle was secured immediately by tightening the string further. The amount of aerosol exiting the distal end of the ETT was obtained by comparing the weight of the bottle before insertion of the ETT and after extraction of the ETT. This procedure was repeated in the normal room air environment (ambient temperature of 24°–26°C) using 4-mm to 8.5-mm ETTs during each test cycle. This cycle was repeated five times, i.e., the amount of aerosols delivered through the ETT was measured five times for each of the five ETTs with different internal diameters.

In the third experiment, we performed the same procedure after adding either one or two connectors to the 15-mm adapter of 4-mm and 5-mm ETTs. The purpose of this was to investigate the capability of these connectors to reduce the delivery efficiency of procaterol aerosol in the treatment of children (Fig. 2).

In the fourth experiment, we performed the same procedure as in the second experiment with 5-mm and 7.5-mm ETTs, but both in the normal room air environment and under humidified conditions, using another MDI. Under humidified conditions, we filled the ETTs with air at 37°C with 100% relative humidity by attaching the ETTs to the outlet port of the humidifier (the temperature and humidity were ascertained by a thermometer- and hygrometer). Subsequently, we inserted the ETT into the bottle and fired the MDI into the 15-mm ETT adapter immediately after detaching the ETT from the humidifier. In this experiment, we measured the total aerosol output per MDI puff in each procedure.

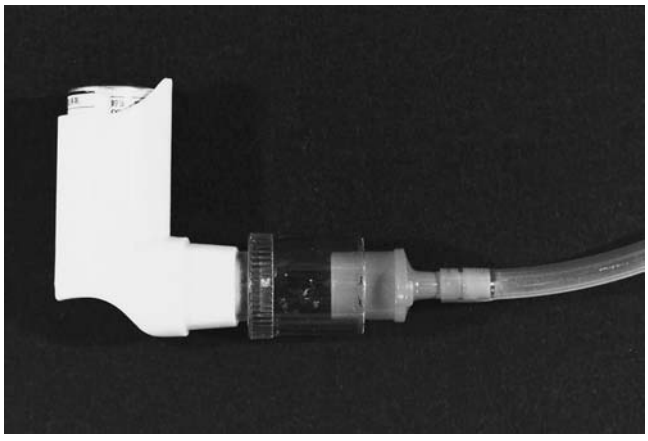

Fig. 2. Photograph of the connector with a standard 15-mm female fitting placed between the 15-mm ETT adapter and the MDI

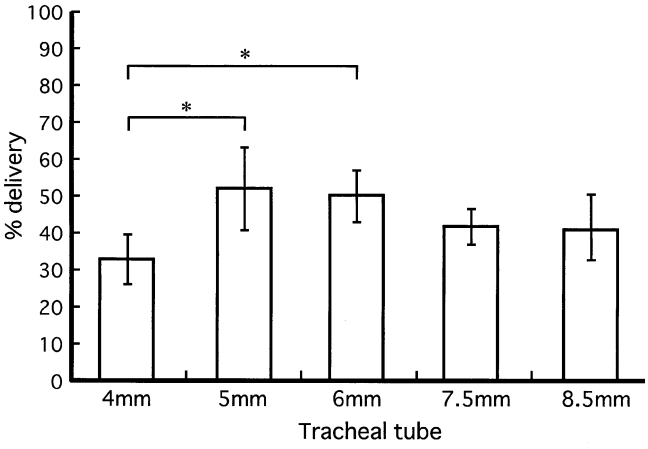

Fig. 3. Percent aerosol delivery of MDI procaterol through ETTs with internal diameters of 4 mm, 5 mm, 6 mm, 7.5 mm, and 8.5 mm. The percent delivery is expressed as a percentage of total aerosol output per MDI puff delivered through the ETT. Values are means ± SD. *Asterisk*, $P < 0.05$, Scheffé's test

All data are expressed as means ± SD. Comparisons of the percent delivery, i.e., the percentage of aerosol delivered through the ETT, among the groups with different ETTs, were performed by analysis of variance (ANOVA) followed by Scheffé's test for multiple comparisons. Comparisons of the delivery percentages among the group without a connector, the group with one connector, and the group with two connectors were analyzed by ANOVA followed by Fisher's Protected Least Significant Difference (PLSD) for a multiple comparison test. An unpaired *t*-test was used to compare the percent delivery in the normal room air environment with that in humidified conditions. Values of $P < 0.05$ were considered statistically significant.

Results

There was no significant difference between the average of the five values obtained as a total aerosol output per MDI puff in the first experiment and the average after the third experiment. Therefore, the mean of the ten values (66.0 ± 2.4 mg) was expressed as the common total aerosol output per MDI puff for calculations of the percent delivery in the second and third experiments.

We calculated the percent delivery of procaterol aerosol by dividing the amount of aerosol delivered through the ETT by the common total aerosol output per MDI puff. The delivery percentages of procaterol aerosol through 4-mm, 5-mm, 6-mm, 7.5-mm, and 8.5-mm ETTs were 32.7% ± 6.6%, 51.7% ± 10.8%, 49.7% ± 7.4%, 40.9% ± 4.2%, and 40.6% ± 9.0%, respectively ($n = 5$ for each ETT) (Fig. 3). Significant differences were found between the 4-mm ETT and the 5-mm ETT ($P < 0.05$) as well as between the 4-mm ETT and the 6-mm ETT ($P < 0.05$).

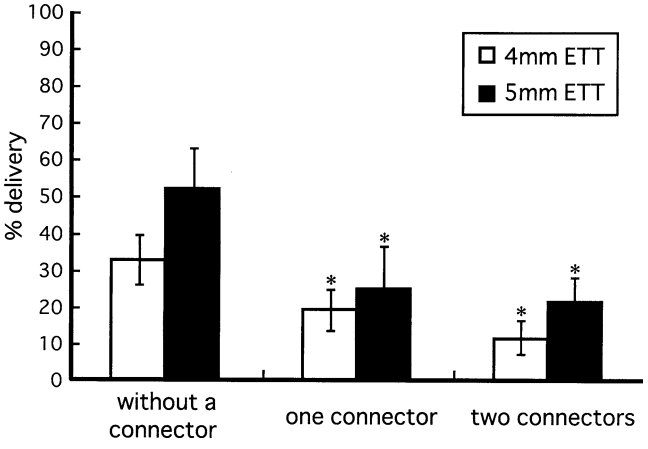

Fig. 4. Percent aerosol delivery of MDI procaterol without a connector, with one connector, and with two connectors, attached to the 15-mm ETT adapter, for the 4-mm ETT and the 5-mm ETT. Percent delivery is expressed as a percentage of total aerosol output per MDI puff delivered through the ETT. Values are means ± SD. *Asterisk*, $P < 0.01$ *vs* without a connector

The percent delivery without a connector, with one connector, and with two connectors for the 4-mm ETT was 32.7% ± 6.6%, 19.0% ± 5.8%, and 11.2% ± 4.6%, respectively ($n = 5$ in each group). For the 5-mm ETT, it way 51.7% ± 10.8%, 24.6% ± 11.8%, and 20.9% ± 7.2%, respectively ($n = 5$ in each group) (Fig. 4). Significant differences were seen between the group without a connector and the group with one connector ($P < 0.01$), as well as between the group without a connector and the group with two connectors ($P < 0.01$) for both ETTs. The percent delivery was greater with

one connector than with two connectors in both ETTs, but the differences were not significant.

The percent delivery was significantly lower under humidified conditions (30.0% ± 10.7% *vs* 45.8% ± 7.6%, $P < 0.05$) than in the normal room air environment with the 5-mm ETT. In the 7.5-mm ETT, delivery was lower under humidified conditions than in the normal room air environment (54.9% ± 5.2% *vs* 61.1% ± 10.9%), but the difference was not significant.

Discussion

The use of the reservoir for aerosol delivery by MDIs makes drug delivery to the lungs more efficient than when the canister is dischanged without use of the reservoir, both in spontaneously breathing patients and in mechanically ventilated patients [1,5]. The droplets decrease in size after evaporation of the propellants in the reservoir [1,6], and the smaller particles are deposited in the more peripheral regions in the lungs [7]. In an emergency situation, however, we may not have enough time to look for the reservoir and place it in line in the anesthesia circuit. We are required to administer the β-agonists to the lungs as soon as possible by firing the MDI directly into the ETT in an intubated patient. Therefore, we attempted to investigate the percent delivery of MDI aerosols through ETTs by firing directly into the 15-mm ETT adapter. Our review of the lung deposition of MDI aerosols in mechanically ventilated patients indicates that it is less than 10% with the use of the MDI plus the MDI actuator/adapter, whereas it is 10%–38% with the use of the MDI plus the spacer [3–5]. In an in vitro experiment, Rau [6] and Crogan [8] reported no more than 10% delivery of aerosol to the distal end of the ETT with the MDI plus MDI actuator/adapter under dry conditions. Rau [6] also found approximately 30% aerosol delivery to the distal end of the ETT with the MDI plus reservoir under the same conditions. Garner [9] compared the percentage of aerosol delivered to the distal end of the ETT in the dry-air phase with that in the humidified-air phase, using a bench model simulating a pediatric mechanical ventilatory circuit. The former was three to five times higher than the latter. Using a bench model with a test lung, Fink [10,11] reported that the percentages of aerosol delivered to the distal ends of the bilateral main bronchi with the MDI plus spacer were 30%–40% under the dry condition and 15%–20% under humidified conditions. Aerosols are more likely to adhere to the wetted inner surfaces of the ETT [12].

In our study, we measured the percent delivery in the normal room air environment in the second and third experiments. The percent delivery was 40%–50% with 5-mm to 8.5-mm ETTs, but it was significantly lower with the 4-mm ETT (33%) than with the 5-mm ETT or the 6-mm ETT. The smaller ETT probably increases the resistance to the flowing aerosol. As a result, the aerosol could spill out of the ETT at the proximal end of the ETT. We compared the percent delivery in the normal room air environment with that under humidified conditions in the fourth experiment, taking into consideration a clinical setting. Whereas the delivery under the humidified condition was 65.5% of that in the normal room air environment with the 5-mm ETT, there was only a slight difference with the 7.5-mm ETT. Water condensation might occupy relatively more space inside the smaller ETT. Even if the humidity and the temperature in the second experiment are taken into consideration, the percent delivery is still higher than expected. We assume the reason that our results revealed a higher percent of delivery compared with the results of other authors is that we did not use the MDI actuator/adapter or a right-angle elbow adapter. Adapters, such as swivel adapters and right-angle elbow adapters, baffle the delivery of aerosol [5,6,8]. Taking into account the rapid evaporation of propellants following the MDI actuation, the actual delivery of procaterol itself through the ETT might be greater than the values obtained in our results.

We thought that the percent deliveries with the 4-mm and 5-mm ETTs might be too high for children. Therefore, we performed the same procedure with the connector placed in line between the ETT and the MDI to investigate whether the connector could reduce the delivery. Attaching one connector to the ETT approximately halved the percent delivery with a 4-mm and 5-mm ETT as compared with the condition without connectors. The ETT has a "spacer" function [8], i.e., large aerosol droplets are retained in the ETT, and their sizes decrease after the evaporation of propellants. A relatively high percentage of the droplets with an aerodynamic mass median diameter (AMMD) of over 3 μm are retained inside the ETT and the large central conducting airways [13]. Deposited particles in the ETT could be drained into the trachea later if the humidity is high enough for condensation of water inside the ETT [8]. We performed this study taking into consideration mechanically ventilated patients without spontaneous breathing. In spontaneously breathing patients, synchronized actuation of the MDI with inhalation would be essential, particularly when the reservoir is not used, although it is not always easy. However, actual clinical experience shows that one or two puffs of β_2-agonist fired directly into the ETT without the reservoir dramatically improve bronchoconstriction. Notwithstanding clinical experience, the percent delivery of MDI aerosol in spontaneously breathing patients is not conclusive, based on this study only.

When we calculated the percent delivery on the basis of the data obtained from the first, second, and third experiments, we used the common total aerosol output per puff 66-mg as the denominator, for simplicity. We recognize that the total aerosol output per puff should have been measured in each procedure of the second and third experiments, and each total aerosol output per puff should have been used as the denominator to calculate each percent delivery. Nevertheless, we do not think that the results in this study were affected to a large extent by adopting the common total aerosol output per puff as the denominator. Most of the differences between the percent delivery calculated on the basis of the common total aerosol output per puff and the percent delivery calculated on the basis of each experimental total aerosol output per puff are expected to be not more than 7%–8% of the latter percent delivery.

In summary, we studied the efficiency of delivery of aerosol of procaterol by MDI through ETTs with five different internal diameters by firing directly into the 15-mm ETT adapter. The percentage of aerosol delivery was 40%–60% in a normal room air environment with 5-mm to 8.5-mm ETTs, but was 33% with the 4-mm ETT. The connector attached to the 4-mm ETT and the 5-mm ETT consistently reduced efficiency of delivery. The percent delivery under humidified conditions with the 5-mm ETT and the 7.5-mm ETT was decreased to 65.5% and 89.8% of that in the normal room air environment, respectively.

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