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Therapeutic Methods

Bronchodilator Effect of Fenoterol and Ipratropium Bromide in Infants With Acute Wheezing: Use Of MDI With A Spacer Device

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Summary. Twenty-eight infants admitted to Exequiel González Cortes Children's Hospital because of acute wheezing (AW) were randomly assigned to three study groups. Fenoterol (FNT), ipratropium bromide (IB), and placebo were administered respectively to children in the different groups by means of metered dose inhalers (MDI) with spacers, using doses of 3 puffs every hour, for 4 hours. The degree of bronchial obstruction was assessed clinically and scored with the single-blind method every hour prior to each treatment. The criterion of a bronchodilator effect was a significant decrease in the degree of bronchial obstruction at subsequent scorings. The scores of the three groups were compared using the Student's t test for matched samples. The same test was also applied to the independent samples for determining the superiority of one treatment, FNT or IB, over the other.

The results indicated a significant decrease in the scores of the groups receiving FNT and IB ($P < 0.05$); this did not occur in the group in which placebo was used. FNT produced a more rapid and sustained effect than IB ($P < 0.05$). Significant bronchodilator effect was obtained in infants with AW when repeated doses of FNT or IB were administered with MDI and spacers. This effect was significantly greater in the group treated with FNT. **Pediatr Pulmonol 1987; 3:352–356.**

Key words: Metered dose inhaler with spacer; infants, average age 10 mos; comparative effectivity by clinical score; single-blind, randomized, placebo-controlled study.

INTRODUCTION

Bronchodilator aerosols, whether administered by wet nebulization or by a metered dose inhaler (MDI) are common treatments for asthmatic patients, producing rapid and efficient relief of bronchospasm with low doses and avoiding adverse secondary effects.[1]

The availability of bronchodilators in MDI, including β_2 agonists or anticholinergics as well as combinations of these has led to an increasing use of aerosols in asthmatic children.[2–4] In order to improve aerosol delivery and to assure deposition of drug particles in the lungs, several inhalation techniques and spacer devices have been designed and studied. The spacers function as aerosol reservoirs between the patient and the MDI. The main purpose of these devices is to avoid impaction of large drug particles in the oropharynx by giving the particles time to evaporate and decrease in size.[5–11]

Among the advantages of MDIs are their small size, making them easy to carry and use, and their delivery of exact doses. Better bronchodilator effect is achieved with the use of a spacer.[3–12] One of the most common causes for hospital admittance of infants and for medical consultations during winter months is acute wheezing (AW). The treatment of AW is still controversial today. The purpose of this study was to evaluate the clinical response to two bronchodilators, FNT and IB, delivered by MDI with a spacer device, for the treatment of hospitalized infants with AW.

MATERIALS AND METHODS

Twenty-eight infants of both sexes were studied. Their average age was 10 months, and they were admitted because of AW. We did not distinguish between asthma

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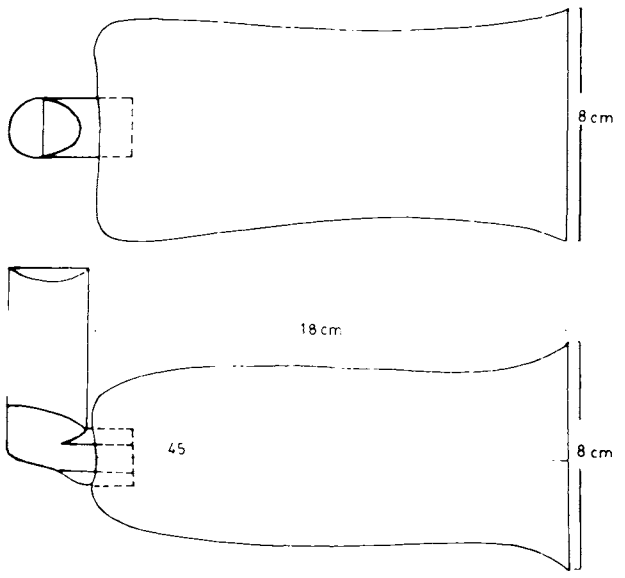

Fig. 1. Schematic diagram of the metered dose inhaler (MDI) with a spacer, viewed from two sides. The principal measurements of the spacer are shown.

TABLE 1—Mean Clinical Severity Scores and Standard Deviations of Bronchial Obstruction in the Three Treatment Groups From the First Hour (Initial) to the Fourth Hour (Final)[a]

	Mean score (SD)		
	Fenoterol (n=)	Ipratropium (n=)	Placebo (n=)
First hour (initial)	8.1 (1.29)	8.7 (0.71)	7.7 (1.22)
Second hour	6.8 (1.14)	7.8 (1.48)	7.3 (1.32)
Third hour	5.9 (0.99)	7.2 (1.48)	7.3 (1.12)
Fourth hour (final)	5.4 (1.07)	7.1 (1.45)	7.4 (1.13)

[a]For statistical comparisons, see text.

and bronchiolitis. The children were assigned, using a table of random numbers, to three treatment groups. Two groups received bronchodilator aerosols, while the third group received an aerosolized placebo.

All of the infants assigned to this study had been admitted because of acute respiratory illness with clinical signs of airway-obstruction, such as audible wheeze, pulmonary hyperinflation, use of accessory muscles during expiration, and increased respiratory rate. Children with cystic fibrosis, congenital heart disease, or history of assisted ventilation during their neonatal period were excluded from the study.

The patients were assigned to groups receiving fenoterol aerosol, ipratropium bromide aerosol, and placebo aerosol. The mean age for the groups was 9 months, 12 months, and 10 months respectively.

FNT, IB, and placebo were administered through an MDI to which a spacer device was attached. The characteristics and measurements of the device are shown in Figure 1.

The open end of the spacer had a diameter adequate to include both nose and mouth and to guaranteee a close fit.

The distance between the MDI and the infant's face, reflecting the size of the spacer, was 18 cm; the volume of the spacer was approximately 480 ml.

The technique for administration of aerosols with MDI and a spacer firmly placed over the infant's face required brief and partial restraint of the child. All of the infants cried when the spacer was applied. The MDI was triggered at the end of an expiration, once every three breaths in an arbitrary manner, three times.

Bronchial obstruction was scored simultaneously by two researchers (J.M. and L.B.), following the single-blind method, every hour for four consecutive hours before administering each treatment.

The Tal[18] scoring system is currently employed in our respiratory unit. We consider it a suitable and objective clinical method for the evaluation of bronchial obstruction in infants. Only infants with scores greater than 6 and equal to or less than 10 were included in this study.

After the final evaluation at the fourth hour, the infants continued receiving bronchodilators as prescribed by their treating physician.

Statistical Analysis

Analysis of variance (ANOVA) was used to establish possible differences among basal scores, Student's t test to compare different scores of the groups while they were being treated, and a t test for independent samples to identify possible advantages of one treatment over the other (FNT and IB).

RESULTS

The initial mean scores of the three groups were similar, and the differences encountered were not statistically significant. This was verified by ANOVA, the result of which was: $F = 1.83$, NS (Table 1, Fig. 2).

The initial and final (fourth hour) assessments for each group were compared. Significant difference between the group treated with FNT ($t = 2.80$, $P < 0.001$) and the group treated with IB ($t = 2.80$, $P < 0.05$) was found. There was no significant change in the group treated with placebo ($t = 0.51$, NS).

No statistically significant changes were encountered between the second and fourth assessment scores for the

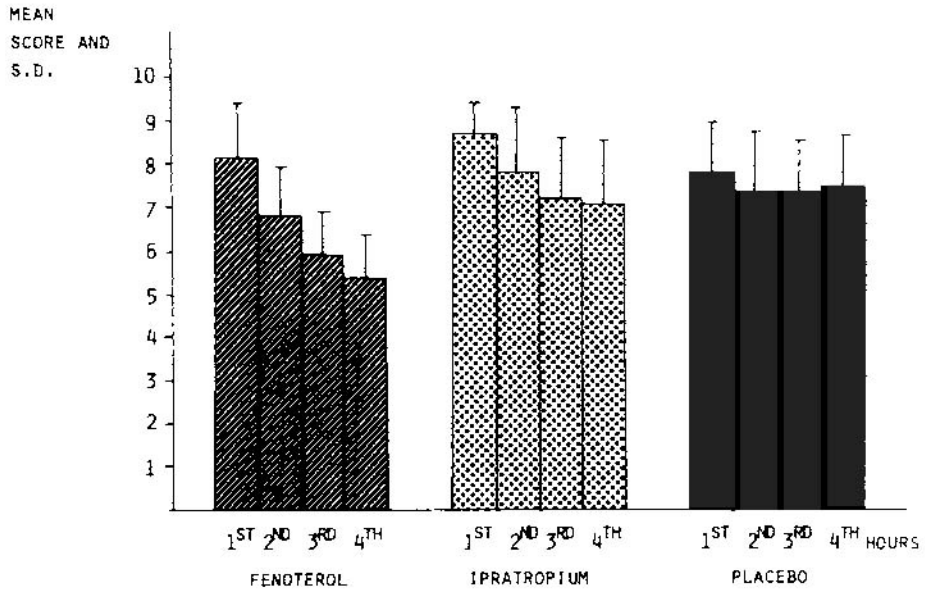

Fig. 2. Mean scores + 1 SD at hourly assessments for the two treatment and the placebo groups. (For statistical comparisons see text.)

group treated with IB. The difference between scores at the second and third assessment was: $t = 1.47$, NS and that of the third and fourth assessment was: $t = 1.00$, NS.

In contrast to these findings, in the group treated with FNT the differences between all assessments were statistically significant: between the first and second, $t = 5.96$, $P < 0.001$; second and third, $t = 3.86$, $P < 0.01$; and third and fourth, or final, assessment, $t = 3.0$, $P < 0.01$. When the t test was applied to independent samples with the aim of demonstrating differences between infants treated with FNT and those receiving IB, bronchial obstruction decreased to a significantly greater extent in the group treated with FNT ($t = 2.07$, $P < 0.05$).

No adverse effects were observed from the use of FNT or IB in any children participating in the study.

DISCUSSION

Various authors have stated that a superior therapeutic effect is obtained when bronchodilators are delivered by MDI attached to spacers for treating asthmatic children.[3,10,11] Nevertheless, their use on infants with AW had not been studied. We believe that this was mainly due to the hypothetical and practical inconveniences their users might have had. Small infants undoubtedly would not comply with recommendations for correct usage of MDI with or without spacers.

When appropriately used, the MDI will deposit only 10% of the administered aerosol in the lower airways. This percentage does not exceed 20% of the dose in adults, even when using a spacer device and optimum inhalatory technique.[13,14]

Unfortunately, a considerable percentage of asthmatic adults and even more children do not employ an adequate technique when using MDI. This may be due to the patient's inability to coordinate the MDI actuation with inspiration. Younger patients may even reject the MDI because of the bitter taste of aerosols. The spacer devices, whatever their size or shape, provide a closed space between the MDI and the patient, allowing time for the particle size of the aerosol to be reduced, which makes it more "respirable." They successfully avoid hand-breath coordination problems, and generally produce better bronchodilator effects.[15-17] In small children the spacer allows the person who administers the aerosol to choose the precise moment during the respiratory cycle for triggering the MDI. This is an obvious advantage over MDI without spacers.

We have used spacer devices such as those illustrated in Figure 1 for years. They are modified saline or glucose containers, are used for IV infusions, and are made of a soft, transparent, plastic material. We adapted the containers by cutting off one end and dilating it by heating until a round shape was attained. The other end has an oval shape and a small opening where the mounthpiece of the MDI is kept firmly in place. The size of the open end is such that when the spacer is placed onto the child's face, both the nose and mouth are covered by the device. When an aerosol is administered to an infant, one must take into account that crying favors inhalation. Most

infants cry when the spacer is applied to their face. It is necessary to determine the length of the expiration by observing the child briefly during crying. The MDI should be triggered at the end of three expirations, keeping the spacer continuously in place. We used the technique described in infants with AW who were hospitalized, as well as in those receiving bronchodilators by MDI as out-patients.

None of the patients treated in this manner had adverse reactions. This is probably due to the fact that the dose reaching the lower airways is minimal. As stated before, under the best inhalation conditions, with the use of the spacer, only 20% of the administered dose will be deposited in the lungs of adults. It is easy to imagine that this percentage is markedly reduced when aerosols are administered to infants, who not only are uncooperative, but vigorously reject the whole procedure.

We believe that when treating bronchial obstruction in infants, doses of bronchodilators, either β_2 agonists or cholinergic antagonists, need to be more frequently administered (and probably at higher doses than those recommended at present), in order to achieve a good bronchodilator effect. We suspect that there is less stress when this procedure is used, in comparison with the use of jet nebulizers, probably because of its shorter duration. Nebulization takes about 10 minutes, while the administration of bronchodilators with MDI take 2 minutes or less.

Some studies suggest certain advantages of the MDI with spacer over nebulizers to achieve bronchodilator effect.[3] Doses given from a nebulizer are conventionally higher than those given from an MDI; for instance, the standard dose of FNT is 400μg from an MDI, but 150μg to 2.5 mg from a nebulizer; the dose of IB is 40μg from an MDI, but 250μg from a nebulizer. Nebulizers are often used in severe, acute attacks, or in hospitalized patients with severe bronchial obstruction who need high doses of bronchodilators for effective therapy. Also, jet nebulizers allow the use of oxygen to generate aerosol, which can be particularly useful for severely ill patients. Furthermore, nonfixed combinations of bronchodilator drugs, like β_2 agonists with cholinergic antagonists in high doses, appear to be more easily provided with a nebulizer than with MDI. While it is feasible to administer high doses by MDI, even the small doses currently used achieve a significant bronchodilator effect.

In this study, higher than usual doses have been employed. Three puffs of FNT or IB were given consecutively every hour for 4 hours, without unacceptable side effects. This regimen resulted in a significant improvement in the signs of bronchial obstruction; bronchodilation can probably be achieved in wheezy infants with more frequent and higher dosages than recommended at the present time.

Whichever the selected aerosol delivery system, either MDI with spacer or nebulizer, it should be correctly used for achieving optimal drug delivery to the lower respiratory tract. In children, and especially in infants, the procedure will have to be adapted individually to each patient's condition and characteristics.

We feel that MDI with spacer may be more readily used than a nebulizer, needing less time for delivering a precise dose and minimizing deposition in the upper respiratory tract. High doses can also be given by MDI. Furthermore, this aerosol delivery device is portable, inexpensive, does not require energy or compressed gas to operate, and parents or persons providing care for these wheezy infants can be easily instructed in its use.

Therefore, bronchodilator drugs given by MDI with spacer could be considered the first choice of treatment for infants with acute wheezing, either during acute attacks during hospitalization, or in recurrences. However, the exact place of MDI and nebulizers in the spectrum of treatment for wheezing infants remains to be established.

The majority of patients in this study who received bronchodilators had considerably lower severity scores by the fourth hour of treatment. Had they been subjected to this modality of treatment in the emergency ward, possibly many would not have required hospitalization.

In conclusion, the results of this single-blind, randomized, placebo-controlled study in infants with AW indicate that both FNT and IB delivered hourly by MDI with spacer, significantly diminished the signs of bronchial obstruction within a short period of time. This did not occur in the placebo group, in which no improvement was observed. FNT had a more evident and sustained bronchodilator effect than IB, as observed by others, both in adults and in children. FNT and IB by MDI with spacer can be considered a safe and efficient alternative therapeutic modality for infants with AW. The comparative advantages over other treatment modalities need to be evaluated in future studies.

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