

# Original salbutamol versus similar salbutamol in children with asthma exacerbation.

## A randomized, controlled, double-blind study

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### SUMMARY

**Introduction.** There is clinical evidence suggesting that original salbutamol is more effective than a similar salbutamol product to revert symptoms in acute asthma exacerbation.

**Objective.** To evaluate the bronchodilator response of both salbutamol medicinal products in children with asthma and to establish, based on the forced expiratory volume, if there is a difference between the group treated with the original salbutamol and the group treated with similar salbutamol.

**Design.** Prospective, randomized, controlled, double-blind study.

**Material and Methods.** One hundred and twenty six children (63 boys, age  $9.18 \pm 2.83$  years old) were included. They were administered a dose of 20 drops (5 mg) of the original salbutamol or similar salbutamol product in nebulizing solution diluted only once in 2 ml saline solution. Pre- and post-bronchodilator, intra- and inter-group forced expiratory volume was compared at baseline and at 30 minutes. The weight of salbutamol drops was determined by gravimetry, the concentration by chromatography and the number of drops by bottle.

**Results.** The bronchodilator response between the pre- and post-bronchodilator forced expiratory volume was 225 ml (95% CI: 164-286) and 224 ml (95% CI: 163-284) for original salbutamol and similar salbutamol, respectively ( $p < 0.001$ ). The Delta difference was 1.3 ml (95% CI: -86+83) ( $p = 0.97$ ). The mean, standard deviation and variation coefficient percentage of the weight of the drop was 364.75 mg ( $\pm 6.01, 1.65$ ) and 543.88 mg ( $\pm 56.09, 10.31$ ) ( $p < 0.001$ ) for original salbutamol and similar salbutamol, respectively.

**Conclusion.** There were no differences in the bronchodilator response measured by FEV<sub>1</sub> between the original salbutamol and a similar salbutamol product.

**Key words:** asthma, beta-adrenergics, generic drugs, pulmonary function, therapeutic equivalence.

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### INTRODUCTION

Asthma, the most frequent chronic inflammatory disease in childhood, may initiate airway obstruction in genetically predisposed subjects exposed to physical, infectious, chemical and pharmacological stimuli.<sup>1,2</sup>

It is a leading cause of school absenteeism and physical activity restriction; it might have a negative impact on the quality of life and, in the public health arena, its treatment results in high costs to the health care system.<sup>3,4</sup> The International Study of Asthma and Allergies in Childhood (ISAAC) revealed that the prevalence of asthma in Argentina is within intermediate values in relation to other countries, accounting for 16% in children between 6 and 7 years old and 11.5% between 13 and 14 years old.<sup>5</sup>

Asthma flare-ups are a frequent cause of visit to the emergency department.<sup>6</sup> According to data provided by the Outpatient Emergency Ward of Hospital de Niños "Ricardo Gutiérrez", 9567 consultations were due to respiratory diseases between June and August, 2010, out of which 1202 (12.6%) were because of asthma attacks.

Although the diagnosis of asthma is clinical, pulmonary function tests are generally used to confirm the diagnosis, monitor the progress of the disease and its response to treatment. Spirometry is the most widely used test, and the forced expiratory volume in 1 second (FEV<sub>1</sub>) is employed to measure the degree of airway obstruction. An increase of more than 15% after the administration of a bronchodilator is highly suggestive of asthma.<sup>7</sup>

Salbutamol is the cornerstone of rescue therapy for acute asthma attacks and is widely used given its proven efficacy and safety.<sup>8,9</sup>

Due to the economic crisis that hit Argentina in 2001, the government issued a formal decree announcing a

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National Health Emergency<sup>10</sup> and the prescription of generics or international common denomination (ICD) drugs was implemented.<sup>11</sup> As a result, there has been an increase of trademarks for the drug salbutamol, with 25 brand names being marketed in the country today.<sup>12</sup>

The hypothesis of this paper arises from the observation that original salbutamol would be more effective than similar salbutamol to revert symptoms of asthma exacerbation.<sup>13</sup> The importance of discussing this subject is based on the need of obtaining clinical and functional evidence to determine if there are differences between these products as far as their efficacy. The objective of this study is to evaluate the bronchodilator response (BDR) of both salbutamol medicinal products in children with asthma and to establish, based on the forced expiratory volume (FEV1), if there is a difference when comparing the original salbutamol group to the similar salbutamol group.

#### POPULATION AND METHODS

A comparative, prospective, randomized and double-blind study was performed in the Outpatient Emergency Ward of Hospital de Niños "Ricardo Gutiérrez" at Buenos Aires between March 2005 and September 2008. This is a university-associated tertiary care hospital with 331 beds, where annually, 110,000 patients are assisted at the Outpatient Emergency Ward. The study included children of both sexes, with ages ranging from 6 to 14 years old, a diagnosis of asthma as per the Global Initiative for Asthma (GINA) guidelines,<sup>14</sup> arterial oxygen saturation >92% and flare-up of the disease with a baseline FEV1 value >50% and <80% of the Polgar child predicted value.<sup>15</sup> This value was determined by a spirometry based on the American Thoracic Society guidelines,<sup>16</sup> with a spirometer called Spirotrac III, a registered trademark of Vitalograph Ltd. (California, USA).

Patients who used short-acting  $\beta$ 2-adrenergic agonists 4 hours prior to consultation and long-acting  $\beta$ 2-adrenergic agonists 12 hours prior to consultation, oral corticosteroids in the last 30 days or who suffered any other chronic pulmonary disease were excluded.

Selected patients were randomized by means of a random number table with assignment codes concealed in consecutive, opaque envelopes. To maintain the double blinding, neither the researchers responsible of the clinical assessment and functional tests nor patients

were aware of the dosage form administered by the nurse.

The treatment was administered in nebulizing solution using a PARI LCD<sup>®</sup>jet nebulizer with a mouthpiece powered by an oxygen flow rate of 8 L/min. Twenty drops of salbutamol were administered as a single dose, once. According to the package insert of both medicinal products, these 20 drops corresponded to 5 mg of the drug, diluted in 2 ml of saline solution. We used the generic salbutamol with brand name Salbutral<sup>®</sup> (Laboratorio Cassará, Buenos Aires, Argentina), approved by the Drug, Food and Technology Administration of Argentina (*Administración Nacional de Medicamentos, Alimentos y Tecnología, ANMAT*). The study drug, the spirometer to perform the functional tests and the nebulizers were provided by the principal investigator, purchased with the PI's personal funds.

The primary efficacy outcome was the comparison of FEV1 at baseline and at 30 minutes after administering the nebulization.

Additionally, we determined the following:

1. The weight in milligrams (mg) of original salbutamol and similar salbutamol drops by means of gravimetry.<sup>17</sup> A precision scale (Mettler, model H2OT, Zurich, Switzerland) was used and 10 drops from 4 bottles of original salbutamol and similar salbutamol were consecutively weighed, and the weight of the 20 drops in each bottle was averaged.
2. The concentration of original and similar salbutamol was measured by high performance liquid chromatography (HPLC).<sup>18</sup> Three aliquots of 5 bottles of each medicinal product were injected with a 1/1000 dilution.
3. The number of drops per bottle, determined with a metered dropper by direct count in 3 bottles of original salbutamol and 3 bottles of similar salbutamol.

The approval of the Teaching and Research Board and the Ethics Committee of the Hospital was obtained.

The tutor's written informed consent was obtained. Afterwards, the study results were reported to the Drug Surveillance Department of the ANMAT.

#### Statistical Analysis

A pilot test which included 65 patients in 2 treatment groups was done to estimate the sample size and to establish, in each group, the mean BDR by means of the Delta product of the difference between the pre-broncho-

dilator (pre- $\beta_2$ ) and the post-bronchodilator (post- $\beta_2$ ) FEV1, and its corresponding standard deviation (SD). The value was 317 ml (95% confidence interval [CI]: 214-421) in the group that received original salbutamol and 258 ml (95% CI: 165-352) in the group that received similar salbutamol. The Student's t-test for paired data showed a statistically significant difference for each drug ( $p < 0.001$ ). Then the BDR Delta difference between groups was determined by the Student's t-test for independent samples, which was 59 ml (95% CI 20-84),  $p = 0.41$ .

Considering a FEV1 difference of 100 ml between both medicinal products as clinically relevant, a SD of 20 ml, a level of statistical significance of 0.05 and a power of 90%, a sample size of 62 patients in each group that received original salbutamol or similar salbutamol was determined.

The study population characteristics were as follows: age, sex, allergic rhinitis, atopic dermatitis and treatment with inhaled corticosteroids. The characteristics were defined based on the Student's t-test or chi-square test, as appropriate.

FEV1 was compared in the same fashion as in the pilot study.

For the statistical analysis of the weight, concentration and number of drops per bottle, mean values, SD and coefficient of variation percentage ( $CV\% = SD/\text{Mean} \times 100$ ) of original and similar salbutamol were compared with the Student's t-test.

Data were processed with the Stata 8.0 software.

## RESULTS

The eligible population was 180 patients out of a total of 5477 visits because of asthma attacks in patients younger than 18 years old. Fifty four patients were excluded because their functional test was out of range (35 with a FEV1  $>80$  L/s, 15 with a FEV1  $<50$  L/s) and 4 because an inadequate technique was used in the functional test. A total of 126 patients, 63 per group, met the inclusion criteria.

Table 1, describes the demographic and clinical characteristics of the studied population; there were no significant differences between the groups.

Regarding the primary efficacy outcome, the bronchodilator response between the pre- $\beta_2$  and post- $\beta_2$  FEV1 was 225 ml (95% CI: 164-286) and 224 ml (95% CI: 163-284) for both comparisons ( $p < 0.001$ ) (Table 2). The BDR Delta between groups was determined. It was 1.3 ml (95% CI: -86 + 83),  $p = 0.97$ . After being treated with the standard treatment for asthma attacks, all patients recovered clinically and none required hospitalization.

The weight of the drops was ( $X \pm SD$ ) 364.75  $\pm$  6.01 mg, and 543.88  $\pm$  56.09 mg, for original salbutamol and similar salbutamol, respectively ( $p < 0.001$ ). The CV% of the means of the drop

TABLE 1. Demographic and clinical characteristics of the population

Variable	Original salbutamol (n= 63)	Similar salbutamol (n= 63)	P
Sex (M/F)	29/34	34/29	0.37
Mean age, in years*	9.08 ( $\pm$ 2.7)	9.28 ( $\pm$ 2.9)	0.67
Allergic rhinitis	8/63	9/63	0.07
Atopic eczema	2/63	3/63	0.2
Prophylaxis with inhaled corticosteroids	11/63	10/63	0.2

\* Values expressed in  $X \pm SD$ . X: mean. SD: standard deviation.

TABLE 2. Intra- and inter-group bronchodilator response of original salbutamol and similar salbutamol

	Pre- $\beta_2$ VEF1 L/s (95% CI)	Pos- $\beta_2$ VEF1 L/s (95% CI)	Bronchodilator Response ml/s (95% CI)	Intra-group pre- and pos- $\beta_2$ *	Inter-groups pre- and pos- $\beta_2$ **
Original salbutamol (n= 63)	1.37 (1.24-1.50)	1.60 (1.44-1.76)	225 (164-286)	$p < 0.001$	$p 0.97$
Similar salbutamol (n= 63)	1.36 (1.22-1.50)	1.58 (1.41-1.75)	224 (163-284)	$p < 0.001$	

\* Student's t-test for paired data.

\*\* Student's t-test for independent samples.

weight was higher in the similar salbutamol group (10.31%) than in the original salbutamol group (1.65%). No statistically significant difference was found in the concentration nor in the CV% between both medicinal products.

The number of drops per bottle was ( $X \pm SD$ )  $465.33 \pm 8.32$  and  $330 \pm 61.79$  for original salbutamol and similar salbutamol, respectively ( $p = 0.02$ ) (Table 3).

## DISCUSSION

A problem that arises at the time of prescribing a medicine as part of a cost-effective strategy is the replacement of original medicines by similar products. It is necessary to have available scientific evidence so as to determine, by means of bioequivalence studies, that a similar active ingredient has the same pharmacokinetic performance than the original product.<sup>19</sup>

Original salbutamol is the active ingredient with which these comprehensive research and development have been made and which has contributed with its own treatment safety and efficacy data. The manufacturing pharmaceutical laboratory (GlaxoSmithKline S.A., Buenos Aires, Argentina) is the owner of the drug rights, this drug is marketed under a trademark name (Ventolin®). A similar salbutamol product or a copy is the medicinal product offered in the market after the original drug has been released. It has the same active ingredient but does not have its license. It meets the same quality criteria as those of the original medicine and its safety and efficacy data are based on the active ingredient background material, but does not have its own research or development.

In Argentina, based on the health risk classification adopted by the ANMAT, salbutamol is included in the group of drugs with a low health risk, which means that the new brands offered to the market do not require bioequivalence studies.<sup>20</sup> Therefore, randomized, controlled clinical

trials have been proposed to determine the therapeutic equivalence through the acute pharmacodynamic response. The BDR obtained by means of pulmonary function tests has been used with this aim.<sup>21-23</sup>

In this study, a significant BDR was observed in both groups, comparing the post- $\beta_2$  to the pre- $\beta_2$ FEV1; however, no significant differences were found as far as the BDR effect size between both groups.

Few papers have been published comparing the efficacy of original salbutamol to that of similar salbutamol for the treatment of acute asthma.<sup>13,23</sup> Astudillo et al.<sup>24</sup> performed a randomized, double blind study to compare the efficacy and safety of the original salbutamol to a generic spray salbutamol, in children with acute bronchial obstruction. They concluded that the generic salbutamol used had no differences as far as efficacy and safety is concerned, with respect to the original salbutamol. However, different to our study, children younger than 2 years with acute obstructive bronchial syndrome were included and clinical parameters were used instead of pulmonary function tests.

Given that the results of our study challenge the clinical observation that gave rise to this hypothesis, the objective was to identify the possible factors that could account for the results obtained.

First of all, a possibility to be considered is the lack of power of the study because the sample size is small. In the pilot study, the sample size determined by the statistical analysis was 62 patients per group and, therefore, we consider that the statistical power of the sample was sufficient.

Secondly, the BDR of salbutamol might vary for different factors.<sup>25,26</sup> The randomized design enabled to homogenize the populations and minimize confounding effects that might modify the response to salbutamol.

TABLE 3. Number of drops per bottle of original and similar salbutamol

	Original salbutamol Number of drops	Similar salbutamol Number of drops	p
Mean	465	330	0.02
SD	8.32	61.79	
CV%	1.78	18.72	
Number of doses per bottle*	23.25	16.5	0.02

SD: standard deviation; CV%: coefficient of variation.

\* A dose is equivalent to 20 drops of salbutamol.

Thirdly, the likelihood that the dose administered of both medicinal products was higher than necessary to obtain the maximum BDR should be taken into account.<sup>27</sup> For similar salbutamol, the dosage is prescribed in drops based on the age and body weight; and for original salbutamol, in mg/kg of body weight. In our study, a single dose of original salbutamol and similar salbutamol was used and therefore, it was not possible to establish in which part of the dose response curve lays the obtained BDR. Although it is possible that the dose prescribed was higher than necessary to reach the maximum BDR, the amount of administered drops reflects the dose typically used in the emergency department for the treatment of an asthma attack.

Finally, the pharmacological test was done to compare the weight, concentration and number of drops per bottle. Even though salbutamol concentration was the same in both forms, there were significant differences in the weight and number of drops per bottle. The weight of the drops was 33% higher in the similar salbutamol product used in comparison to the original drug. It is worth pointing out that the original salbutamol has a metered dropper that enables to precisely determine the number of drops, while similar salbutamol used in this study does not have a dropper and drops fall by gravity and by the degree of tilting of the bottle which renders the administration of the prescribed dose difficult.

Though in daily practice the dose of salbutamol is calculated based on the number of drops instead of mg/kg of body weight, if the different amounts in milligrams of salbutamol present in the drops of the original and the similar active ingredient are considered, and the differences in the metered dropper, the approach mentioned implies the risk of administering different doses of salbutamol.

## CONCLUSION

In this research study, no significant difference was found in the BDR determined by FEV1 measurement between the original salbutamol and a similar salbutamol product.

Considering the difference found in the weight of the drops, new studies comparing milligrams of salbutamol instead of number of drops will enable to establish if there are differences in the BDR between original salbutamol and similar salbutamol.

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