Hospital General Universitario Gregorio Marañón

SaludMadrid

Comunidad de Madrid

Contrasting Dosivent with Plus Flow Vu Spacer in Bronchial Hiperreactivity Patients

NCT: N/A

Date: 01/march/2022

Doctor Esquerdo, 46
28007 Madrid
www.hggm.es

Contrasting Dosivent with Plus Flow Vu Spacer in Bronchial Hyperreactivity Patients

Inhaled medication is the first-line treatment for diseases such as asthma or chronic obstructive pulmonary disease. Its effectiveness is related to the amount of drug that manages to be deposited beyond the oropharyngeal region, with the place where the deposit occurs and with its uniform distribution or not. Other important factors are the size of the inhaled particles, breathing conditions, airway geometry, and mucociliary clearance mechanisms.

The respiratory system is specially designed both anatomically and functionally, so that the air reaches the most distal territories in the best clean conditions. The hairs of the nose, the heat turbines of the nostrils, the vocal cords, the cilia of the bronchial epithelium, the sneezing and coughing reflexes, etc., contribute to carrying out this work in the most appropriate way.

The size and shape of the particles are essential factors that will determine their deposit in the lung. The size is defined by what is called the diameter of the mean aerodynamic mass (DMMA) or diameter of a particle of mass equal to the median of the particles of a population, that is to say, that diameter of the particle in which 50% of the mass of the aerosol is above it and the other 50% below. Depending on their size and shape, particles can be deposited by four mechanisms:

Shock. It is the physical phenomenon by which aerosol particles tend to continue with their trajectory when they pass through the airways, instead of adapting to the curvatures of the respiratory tract. Particles with sufficient momentum (mass times velocity) will be affected by centrifugal forces at those points where the airflow changes direction suddenly, hitting the airway wall. This happens mainly in the first 10 bronchial generations, in which the air velocity is high and the flow is turbulent. This phenomenon mainly affects particles larger than 10 µm, which will be retained mainly in the oropharyngeal region, especially if the drug is administered using powder inhalers (PSI) or pressurized cartridge inhalers (PCI).

Intercept. It occurs mainly in the case of fibers, in which, due to their elongated shape, the deposition occurs as soon as they come into contact with the airway wall.

Sedimentation. It is the physical phenomenon by which particles with a sufficient mass are deposited by gravity when the time spent in the airway is long enough. It predominates in the last 5 bronchial generations, in which the air velocity is low and, therefore, the residence time is prolonged.

Suspension. It is the phenomenon by which the particles of an aerosol move erratically from one place to another in the airways. It happens as a consequence of the Brownian movement of the particles and occurs in those with a size of less than 0.5 µm of DMMA when they reach the alveolar spaces, where the air speed is practically zero. These particles usually do not settle and are expelled back to the outside with the expiration.

Aerosolized drug particles usually have a uniform shape, with symmetry in several planes and are rarely less than 1µm in size, so the predominant mechanisms will be shock and sedimentation.

In general, it can be considered that particles with DMMA greater than 10 µm are deposited in the oropharynx, those of 5-10 µm in the central airways, and those of 0.5-5 µm in the small airways and alveoli. Therefore, for topical respiratory treatment, it is interesting to use

particles with DMMA between 0.5 and 5 µm. It is what is called the respirable fraction of an aerosol.

One way to avoid miscoordination between the patient and the device is inhalation chambers, which attach to the mouthpiece of the ICP. The aerosol passes into the chamber and the overly large particles hit its walls, being retained in it, while the smaller particles remain in suspension inside the chamber until they are inhaled by the patient. In addition, the space provided by the chamber between the ICP and the patient's mouth allows the aerosol to slow down, reducing the impact against the oropharynx. In this way, local adverse effects are reduced and the pulmonary deposition of the drug is increased. ICPs used with an inhalation chamber have been shown to be as effective as nebulizers in the treatment of acute asthma attacks.

Also, with the aim of avoiding activation-inhalation incoordination, ICPs have been developed that are triggered automatically with the patient's inspiration, such as the Autohaler® and Easybreath®, which have been shown to improve the pulmonary deposition of the drug in patients with coordination difficulties. They also require a lower inspiratory flow than conventional ICPs, around 18-30 L/min, which makes them more suitable for patients with physical limitations, children, and the elderly.

Primary Objectives

- Compare the efficacy, as measured by changes in forced expiratory volume in the first second (FEV1) in miliLiters of inhaled Salbutamol with the Dosivent® chamber versus the widely used Aerochamber Plus® Flow-Vu® in patients with a positive Bronchodilator testing.
- Compare the efficacy, as measured by changes in forced expiratory volume in the first second (FEV1) in percentage of inhaled salbutamol with the Dosivent® chamber versus the widely used Aerochamber Plus® Flow-Vu® in patients with a positive Bronchodilator testing.

Secondary Objectives

- Compare the efficacy, as measured by changes in forced vital capacity (FVC) in miliLiters,of inhaled Salbutamol with the Dosivent® chamber versus the widely used Aerochamber Plus® Flow-Vu® in patients with a positive Bronchodilator testing.
- Compare the efficacy, as measured by changes in forced vital capacity (FVC) in percentage,of inhaled Salbutamol with the Dosivent® chamber versus the widely used Aerochamber Plus® Flow-Vu® in patients with a positive Bronchodilator testing.

Number of Patients

Approximately 50 patients with a diagnosis of Bronchial Hyperreactivity will be included in the study.

Methodology

The investigators are conducting a non-randomized, open-label, crossover-controlled clinical trial in 50 patients with a previous positive bronchodilation testing. The protocol was approved

by the local clinical ethics committee (code 03/2022). All participants provided written informed consent before any study procedure. During the study, the principles of the Declaration of Helsinki and the current standards of Good Clinical Practice were followed.

Participants over 18 years of age are included who attended our center for a bronchodilator test, gave a positive result in this test, and provided written informed consent for participation in this study. Patients are excluded if grade A quality spirometry was not obtained according to the classification in current regulations and, in the opinion of the investigator, performing a bronchodilator test could pose a risk to the patient or interrupting the usual bronchodilator treatment could worsen the underlying respiratory pathology.

Inclusion Criteria:

- Patients over 18 years of age
- Attending our center for a bronchodilator test
- Positive bronchodilator result with increase of Forced Expiratory Volume in first second greater than 200mL and 12%
- Provided written informed consent for participation in this study

Exclusion Criteria:

- Grade A quality spirometry was not obtained according to the classification in current regulation
- Performing a bronchodilator test, in the opinion of the investigator, could pose a risk to the patient or interrupting the usual bronchodilator treatment could worsen the underlying respiratory pathology.

Determination of sample size

To achieve a statistical power of 80% in order to detect differences in the test of the null hypothesis H_0: $\mu_1 - \mu_2 = 0$ for two related samples, with a significance level of 0.05, it will be necessary to include 45 patients in the study. Taking into account that the expected percentage of dropouts is 5%, it would be necessary to recruit 50 subjects for the study.

Statistical Methods

The primary analysis will be performed by intention to treat according to the following table:

Population	Description
All patients included	All patients registered in the study database; includes both screened participants and participants who are not selected but sign the informed consent (IC) form
By modified intention to treat	All randomized patients receiving at least one dose of study treatment. Participants will be analyzed according to the treatment to which they were randomly assigned. The intention-to-

	treat population will be used for all efficacy summaries
Protocol population (PP)	The PP is comprised of the intention-to-treat population, excluding any participant with a major deviation from the protocol. The PP will be used to present sensitivity analyzes for the key endpoints.
Safety population	All randomized participants receiving at least one dose of study treatment. Participants will be analyzed according to the treatment they actually received. The safety population will be used for all safety summaries

Parameter differences will be described as mean and standard deviation if the normality of the mean differences can be verified; otherwise, they will be described as median and interquartile range. The proportions will be described with their standard error.

Study variables will be analyzed using linear mixed models representing repeated measures in which patient will be the random effect and treatment and study phase will be the fixed effects.

Schedule of Activities (SoA)

	Visit 1	Visit 2
Informed Consent	X	
Inclusion and Exclusion Criteria	X	
Medical History	X	
Inhaled Therapy Medication	X	
Randomization	X	
Spirometry with Bronchodilator Testing	X	X
Clinical Registry	X	X

Procedures

Informed consent must be signed prior to any screening assessment.

Patients with Bronchial Hyperreactivity, defined by a positive Bronchodilator Test, will be offered the study through a patient information sheet and informed consent from the patient. A positive bronchodilator test is defined as patients with an improvement in forced expiratory volume in the first second (FEV1) of 200mL and an increase of 12% after 15-30 minutes of application of 4 puffs of Salbutamol in a pressurized cartridge with the Aerochamber Plus Flow air chamber. Vu according to usual clinical practice. Once the patient has signed the informed consent, they will be summoned to perform said test again on another day, having already passed the 6-hour Salbutamol washout period. Subsequently, a comparison will be made with a Delta limit of non-inferiority of 3%.

Bibliography

- Fernandez- Tena A., Casan Clarà P. Depósito pulmonar de partículas inhaladas. Arch Bronconeumol. 2021: 48(7); 240-6.

- Maiz- Carro L., Wagner-Struwing C. Beneficios de la terapia nebulizada: conceptos básicos. Arch Bronconeumol. 2011: 47 (Supl. 6): 2-7

- Byron P. Drug Delivery Devices. Issues in Drug Development. Proc Am Thorac Soc Vol 1. Pp. 321-328, 2004.

- García Río F, Prados Sánchez C, Villamar León J, Álvarez-Sala Walter R. Aerosoles, inhaladores, nebulizadores y humidificadores. Bases teóricas y aplicaciones prácticas de la aerosolterapia y de la ventiloterapia. Medicine. 1997;7:1779–85.