EFFICACY OF DOXOPHYLLINE AS A SPARING TREATMENT FOR INHALED CORTICOSTEROIDS IN MEXICAN CHILDREN WITH ASTHMA.

1. BACKGROUND

Asthma is a chronic inflammatory disease of the airways in which many cells participate, particularly, mast cells, eosinophils, T lymphocytes, neutrophils, epithelial cells and their mediators. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, dyspnea, chest tightness and cough, particularly at night. These episodes are usually associated with a generalized, variable and reversible airflow obstruction.[1]

Inhaled corticosteroids (ICS) are first-line drugs for the treatment of persistent asthma. The effectiveness of existing ICS is excellent; however, a number of questions remain regarding its possible adverse effects, despite the fact that the use of the inhalation route has allowed the minimization of the systemic exposure to these drugs.[2]

Some patients who do not respond adequately to the ICS, usually do not administer them due to steroid phobia among the parents of asthmatic children, or there is little adherence to inhaled treatment. Methylxanthines are widely used in the treatment of asthma. It is one of the few medications for asthma that can be administered orally. They are useful especially in patients who cannot adapt to inhaled medications. Methylxanthines are unique in exhibiting dual-function properties by inducing bronchodilation and having anti-inflammatory and immunomodulatory effects. Theophylline is the oldest methylxanthine and non-specificly inhibits phosphodiesterase, it is a little used drug because it has many adverse effects with lower therapeutic index. 3

Doxophylline is a drug of the family of methylxanthines, with a similar efficacy compared to theophylline when applied in the treatment of various respiratory diseases, but with better tolerability profile. Doxophylline has been shown to be a bronchodilator and anti-inflammatory drug with a wider therapeutic window than other methylxanthines.[4] It has been suggested that lower affinity towards adenosine receptors (A1 and A2) may explain its better safety profile. In addition, unlike theophylline, doxophylline does not antagonize calcium channel blocking receptors, nor does it interfere with the influx of calcium into cells.[5]

Doxophylline produces stable serum concentrations, so its plasma monitoring is only required in patients with hepatic insufficiency and intolerance to methylxanthines. The maximum effects of both, theophylline and doxophylline, are observed at 6 weeks for asthmatic patients and at 8 weeks for adult patients with COPD.[4]

Clinical studies have reported that doxophylline is more effective in improving lung function tests in adults and children, as well as in decreasing clinical symptoms, reducing the incidence of adverse effects and the need of emergency bronchodilators, with a better profile in terms of safety.[1,2] In murine models, developed by Riffo-Vasquez

et al., it has been demonstrated that doxophylline potentially reduces the need for corticosteroids, which was also observed in other clinical studies. [6,7,8]

2.- PRIMARY OBJECTIVE

To evaluate the efficacy of doxophylline in reducing the use of inhaled corticosteroids in Mexican children with asthma.

3.- SECONDARY OBJECTIVES

- To demonstrate the anti-inflammatory effects of low dose corticosteroid treatment in combination with doxophylline in Mexican children with asthma.

- To compare changes in pulmonary function tests during treatment with doxophylline in combination with inhaled corticosteroids.

- To report adverse effects related to the treatment with doxophylline and inhaled corticosteroids.

- To assess the reduction in the need of inhaled rescue medication.

- To evaluate the exhaled breath temperature in Mexican children with asthma treated with doxophylline.

- To determine the level of asthma control in Mexican children during treatment with doxophylline.

4.- ENDPOINTS

Primary Endpoint: Changes in the values of FEV1 (FEV1 in percent predicted) by comparing the baseline to subsequent evaluations.

Secondary Endopoints:

- The use of rescue therapy defined as daily average of inhalations per day according to the data collected in the patient's diaries.

-Differences in values exhaled breath temperature measured in Celsius degrees with the X-halo device, comparing the baseline to follow-up evaluations.

-Differences in clinical asthma control assessment with a visual analogue scale (minimum score is 1, maximum score is 10,) comparing the baseline to follow-up evaluations.

- Differences in the values of fractional exhaled nitric oxide (FeNO) between baseline and subsequent measurements.

-Number of asthma exacerbations defined as acute episodes of progressively worsening shortness of breath, coughing, wheezing, and chest tightness or any combination thereof for at least 3 days, reported on the patient´s symptoms log.

- The use of systemic corticosteroids for at least 3 days for the treatment of an asthma exacerbation according to the data collected in the patient's diaries.

5.- METHODS

A) Study design:

Pilot, open, longitudinal, comparative, prospective and cross-sectional study of parallel groups.

B) Study Population:

1. Number of patients: 60; divided into two groups of 30 patients each according to the age.

   a. Sample size
   Based on the asthma patients prevalence of the Allergy and Clinical Immunology Service of the University Hospital "Dr. José Eleuterio González " with medium or high doses of inhaled corticosteroids and considering a confidence level of 95% and a margin of error of 5%, a sample size of 60 patients is calculated.

2. Population characteristics:

A.- Inclusion criteria:

1. Mexican patients between 6 and 16 years old.
2. Clinical diagnosis of asthma according to the current guidelines of the Global Asthma Initiative (GINA) 2018.
3. Patients with asthma treated with budesonide at medium or high doses during (GINA guidelines´ steps 3 or 4) at least two months before the first study visit. Budesonide medium dose: 200-400 mcg / day (6-11 years) and 400-800 mcg / day (> 12 years). Budesonide high dose: > 400 mcg / day (6-11 years) and > 800 mcg / day (> 12 years).

B.- Exclusion criteria

1. Patients <6 or ≥16 years of age.
2. Patients with <16 kg of body weight.

3. Patients who have had an asthma exacerbation that required treatment with systemic corticosteroids (oral, intramuscular or intravenous) during the 2 months prior to the first study visit.
4. Patients who have presented an asthma exacerbation that required hospitalization during the 2 months prior to the first study visit.
5. Any other chronic lung disease that could impair lung function evaluation.
6. Cardiovascular, infectious, metabolic or neoplastic disease that could interfere with the evaluation of the patient.
7. Current use of drugs that interact with doxophilin: other xanthines, ephedrine or other sympathomimetics, erythromycin, troleandomycin, lincomycin, clindamycin, allopurinol, cimetidine, two months prior vaccination, propranolol, phenytoin or other anticonvulsants.

C.- Elimination criteria:

1. Patients who do not complete the evaluations or study procedures.
2. Patients who technically cannot perform the evaluations or study procedures.
3. Patients who do not wish to continue in the study.

D.- Reference site and recruitment method:

Allergy and Clinical Immunology Service of Nuevo León Autonomous University´s (UANL) Hospital “Dr. José Eleuterio González.”

Patients will be recruited from the outpatient clinic of the Allergy and Clinical Immunology Service of the Nuevo León Autonomous University´s (UANL) Hospital “Dr. José Eleuterio González”, by invitation from the investigator at the time of his routine examination or procedures and through printed and digital advertising media.

C) Study methodology:

By accepting the invitation to participate and signing the informed consent form by the subject's parents and the subject's written consent form, the study will last for three months in which the subject will be randomized to receive a treatment plan during 8 weeks. Patients will be integrated into two groups through simple randomization since both groups will receive both treatment schemes by the end of the study, as it is a cross-over study. The patient and the patient's parents must agree to be able to join one of the groups.

The two groups are: budesonide at the same dose in which the subject is currently treated plus doxophilin at a dose of 18 mg / kg per day, maximum of 800 mg / day (Group A) and a reduced dose of inhaled budesonide plus doxophilin to a dose of 18 mg / kg per day, maximum of 800 mg / day (Group B), for 4 weeks. Low dose of budesonide: 100-200 mcg / day (6-11 years) and 100-400mcg / day (> 12 years).

By adding doxophiline, it will allow us to keep the patient in the same step as the GINA with the one at the beginning of the study and decrease the dose of inhaled corticosteroid and assess the efficacy of doxofiline in conjunction with the reduced dose of inhaled corticosteroid. The steroid decrease in patients in Group B will be performed progressively during 2 weeks in order to minimize adverse events and medication tolerability.

After four weeks of treatment, both groups will interchange their treatment regimen for an additional 4 weeks: budesonide at the same dose in which the subject is at the beginning of the study plus doxophylline at a dose of 18 mg / kg per day, maximum 800 mg / day (Group B) or a reduced dose of inhaled budesonide plus doxophilin at a dose of 18 mg / kg per day, maximum of 800 mg / day (Group A).

The patient will be provided with a flowmeter to perform peak expiratory flow (PEF) measurement in the morning and evening on a regular basis, along with a record of symptoms. The patient will take a morning and evening measurement of the exhaled breath temperature with the X-halo device and record it in the measurement log. The diary will include an action plan in case of exacerbation of the symptoms and the patient will deliver it to the researcher at each visit to analyze the recorded information. A follow-up visit will be made and the subject's participation in the study will be concluded. The subject will be asked to attend 6 scheduled visits to the site, where the following procedures will be carried out:

Visit 1 (W0)
-Full medical history including information on the use of inhaled corticosteroids, asthma exacerbations and the use of rescue medication.
-Full physical examination with anthropometry and vital signs including pulse oximetry and axillary temperature.
-Spirometry with reversibility test according to the guidelines of the American Thoracic Society (ATS).
-Measurement of the temperature of the exhaled breath with the X-halo device.
-Complete Blood Count.
-Fractional exhaled nitric oxide(FeNO).

Visit 2 (W2)
- Complete medical history including asthma exacerbations and use of rescue medication.
-Full physical examination with anthropometry and vital signs including pulse oximetry and axillary temperature.
-Spirometry with reversibility test.
-Measurement of the temperature of the exhaled breath with the X-halo device.
-Record adverse events.
-Fractional exhaled nitric oxide(FeNO).

Visit 3 (W4)

- Complete medical history including asthma exacerbations and use of rescue medication.
--Full physical examination with anthropometry and vital signs including pulse oximetry and axillary temperature.
-Spirometry with reversibility test.
-Measurement of the temperature of the exhaled breath with the X-halo device.
-Record adverse events.
-Review of the patient´s records of PEF, symptoms and breath temperature.
- Fractional exhaled nitric oxide(FeNO).
-The change of the treatment plan will be made according to the branch in which the subject was included.

Visit 4 (W6)
- Complete medical history including asthma exacerbations and use of rescue medication.
-Full physical examination with anthropometry and vital signs including pulse oximetry and axillary temperature.
-Spirometry with reversibility test.
-Measurement of the temperature of the exhaled breath with the X-halo device.
-Record adverse events.
-Review of the patient´s records of PEF, symptoms and breath temperature.
- Fractional exhaled nitric oxide(FeNO).

Visit 5 (W8)
- Complete medical history including asthma exacerbations and use of rescue medication.
-Full physical examination with anthropometry and vital signs including pulse oximetry and axillary temperature.
-Spirometry with reversibility test.
-Measurement of the temperature of the exhaled breath with the X-halo device.
- Blood count with differential.
-Review of the patient´s records of PEF, symptoms and breath temperature.
-Fractional exhaled nitric oxide (FeNO).
-Treatment between week 8 and the follow-up visit will be prescribed based on the investigator´s discretion.

Visit 6 (Follow-up W10-12)
-Complete medical history including asthma exacerbations and use of rescue medication.
-Full physical examination with anthropometry and vital signs including pulse oximetry and axillary temperature.
-Spirometry with reversibility test.
-Measurement of the temperature in the exhaled breath with the X-halo device.
Asthma control test (ACQ-IA) and visual analogous scale of symptom control.
-Record adverse events.
-Review of the patient´s records of PEF, symptoms and breath temperature.

- Fractional exhaled nitric oxide (FeNO).

6.- STATISTICAL ANALYSIS

For the purposes of data analysis, age groups of 6-11 and 12-16 years old will be conducted. The continuous variables will be described with means and standard deviation, for the categorical variables, percentages and frequencies will be used. The continuous variables will be compared with Student's t-test for related samples in the case of having a normal distribution, or with Wilcoxon in the case of non-parametric variables, for the comparison of more than 2 groups ANOVA or H of Kruskal Wallis will be used. The dichotomous variables will be analyzed using Chi square or Fisher's exact test in the case of 2x2 tables. The statistical analysis will be performed with IBM SPSS version 20 (SPSS, Inc., Armon, NY).

7.- REFERENCES

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