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ORIGINAL ARTICLE

Standardizing selection criteria in nasal medication studies

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Summary

Clinical studies on nasal topical medications require the standardization of "nasosinusal normality" in order to establish control groups through a specific evaluation of the upper airways. **Aim:** to standardize the evaluation of candidates for control groups in clinical studies on nasal topical medications. **Material and Methods:** healthy male volunteers of 18 to 50 years of age, asymptomatic from the nasosinusal standpoint were subjected to a sequential and excluding assessment made up of clinical evaluation, immediate hypersensitivity skin test, saccharin test, flexible nasofibroscopy and nasal cytology. **Study design:** Cross-sectional contemporary cohort. **Results:** Of the 33 people originally enrolled, 14 (42.4%) were excluded for clinical reasons. Of the 19 remaining, 2 (10.5%) had atopy diagnosed in the skin test and were excluded. 17 were tested with saccharin and presented normal mucociliary clearance. Evaluation by nasal endoscopy showed abnormality in 2 cases (11.8%) and these were excluded. The remaining 15 were submitted to nasal cytology, which proved normal, representing 45.5% of those initially included. **Conclusion:** The proposed protocol for sequential and excluding evaluation was effective in defining candidates for the establishment of control groups in clinical studies on nasal topical medications.

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INTRODUCTION

Nasosinusal physiology is important for promoting quality of life and preventing respiratory disease, especially in large cities, where there are many aggressors to the respiratory mucosa, such as low atmospheric humidity, a high concentration of pollutants, and indiscriminate use of air conditioning systems.[1] Diseases such as rhinitis, sinusitis, and airway viral infections reach high prevalence and morbidity rates among these populations, leading to other even more severe conditions, such as asthma, bronchitis, pneumonias, and emphysema.[2] Topical nasal medication aims to clean and hydrate the mucosa (saline solutions,[3,4] nasal gel,[5-7] and ringer lactate solution[8]) and to administer corticosteroids topically.[6] It is also possible to use this route for systemic drugs, given its extensive capillary network.[9] Controlled clinical studies are thus needed to demonstrate the efficacy and safety of drugs given by this route.

Characterizing "normal" or healthy subjects nasosinusally is important in studies of topical nasal drugs, both for PHASE 1 trials, which classically include healthy subjects, and in PHASE 2, 3 and 4 trials, in which it is necessary to confirm the nosological entity being studied and control groups.[10] In defining a control group, it is necessary to make sure that subjects have no systemic diseases that might affect their general health; such diseases included arterial hypertension, diabetes mellitus, and chronic renal failure. Additionally, factors that may interfere pharmacologically with the drugs being studied - such as use of other medications - should be excluded.

The gender and age of subjects should also be considered, since female hormones, for instance, may affect the nasal mucosa, altering nasosinusal physiology,11 and elderly populations may present typical changes of ageing in the nasal musoca.[9] For this reason, most of the clinical trials for evaluating topical drugs chooses adult males as their study populations, except when the study drug is specifically indicated for the female, pediatric or elderly populations. Environmental conditions may also affect such choices;[1,9,12] geographically distant populations may be exposed to very different conditions of air humidity, temperature, presence of pollutants, and irritative or allergenic agents, which compounds the difficulties of standardizing control groups and characterizing a healthy nasal mucosa.[1,9,12]

Anatomical features of the nose, such as septal deviation, turbinate hypertrophy, or polyps, and a history of surgery or recent airway infections, may also interfere with nasosinusal physiology. Other factors should also be taken into account, such as smoking, medication or use of illegal drugs by a nasal route.

We conducted a survey of nasosinusal conditions of a population declared as healthy and asymptomatic, recruited at a research center in the city of Campinas, Sao Paulo state, to define a test protocol aiming at standardizing and demonstrating a status of nasosinusal health and "normalcy", and to define selection and exclusion criteria for research subjects in clinical trials using topical nasal medication. We wrote a protocol that comprises a careful clinical evaluation, a sequential and excluding immediate hypersensitivity skin test, the saccharine test, flexible nasofibroscopy, and a nasal cytogram.

METHOD

This study was undertaken at the Scentryphar Pesquisa Clínica Ltda research center located in the city of Campinas, Sao Paulo state, with funding from Libbs Pharmaceutical Ltd, and conforming to Brazilian and international guidelines for good clinical practices, established by the International Harmonization Conference (GCP - ICH), and also in conformity with the Helsinki Declaration principles defined by the World Medical Association (WMA). The Institutional Review Board of the Medical Science School, Campinas University - UNICAMP approved this study (number 1.046/2007). A free informed consent form was made in line with institutional requirements and applied to subjects that volunteered for this study.

Self-declared healthy, disease-free and nasosinusally asymptomatic male adults aged from 18 to 50 years were invited to participate in this study. A 5-step sequential evaluation was done, as follows:

Step 1: Clinical assessment (CA).

The following inclusion and exclusion criteria were defined in this step: inclusion criteria - healthy, male subjects aged from 18 to 50 years, with no medical history of rhinitis, sinusitis, asthma or chronic bronchitis, able to sign the free informed consent form; exclusion criteria - having participated in any other clinical trial within the past one year, a medical history of upper airway viral infection or sinusitis within the last three weeks, having used any topical nasal medication within the last four week, having taken systemic corticosteroids, antihistaminic drugs or decongestion drugs within the last four weeks, a history of nasal or sinus surgery within the last five years, smoking or a history of smoking within the last five years, daily alcohol consumption and/or having used illicit drugs within the last two years. A general physical examination was also done in this phase, including body temperature, pulse and arterial pressure measurements, and anterior rhinoscopy. Cases not encompassed by the inclusion/exclusion criteria, or with findings in the physical examination, were excluded.

Step 2: Immediate hypersensitivity skin test (HT)

Subjects selected in step 1 (CA) underwent step 2 (HT). Those positive for histamine (positive control) and negative for a 0.9% saline solution (negative control), standard acarid antigens (D. pteronyssinus, D. farinae, B tropicalis), fungi (A. alternata, C. herbarum, A. fumigatus),