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(54) Title: METHODS AND COMPOSITIONS TO TREAT AND DIAGNOSE DISEASES OR PATHOLOGIES ASSOCIATED WITH INFLAMMATION OF THE SINUSES AND NASAL CAVITY

(57) Abstract: Methods and compositions for the treatment of rhinosinusitis in a subject using topical verapamil.

Methods and Compositions to Treat and Diagnose Diseases or Pathologies Associated with Inflammation of the Sinuses and Nasal Cavity

CLAIM OF PRIORITY

This application claims the benefit of U.S. Provisional Application Serial No. 62/823,233, filed on March 25, 2019. The entire contents of the foregoing are incorporated herein by reference.

TECHNICAL FIELD

This invention relates to methods and compositions for the treatment of rhinosinusitis in a subject using topical verapamil.

BACKGROUND

Chronic Rhinosinusitis with Nasal Polyps(CRSwNP) is characterized by the presence of edematous polypoid mucosa and predominantly eosinophilic inflammation[1]. Corticosteroids remain the mainstay of treatment however they are non-targeted and may be associated with dose limiting side effects, even when given topically[2]. Consequently, the development of novel, cost effective, and targeted therapies represents a significant unmet need for patients with CRSwNP.

SUMMARY

Provided herein are methods for treating chronic rhinosinusitis in a subject. The methods include identifying a subject having chronic rhinosinusitis; and administering a composition comprising 5-150 mg verapamil to nasal passages and sinuses of the subject using a high volume, low pressure irrigation with normal saline, wherein the verapamil is administered locally to the subject's nasal passage and sinuses by irrigation with a high volume of saline.

In some embodiments, the subject has chronic rhinosinusitis with nasal polyps.

In some embodiments, the composition is administered one or two times a day, preferably wherein a dose of 10-300 mg/day is administered.

In some embodiments, the volume of saline is 100 or 150ml up to 250 or 300 ml or 500 ml. In some embodiments, the volume of saline is 150 to 250 ml.

In some embodiments, 20 to 120 mg total verapamil per dose is administered, preferably wherein 40-240 mg verapamil is administered per day.

In some embodiments, the subject having chronic rhinosinusitis was identified by endoscopy.

In some embodiments, the subject having chronic rhinosinusitis was identified by computed tomography.

In some embodiments, the subject having chronic rhinosinusitis was identified by observing the subject's symptoms and duration of symptoms.

In some embodiments, the methods include monitoring the efficacy of the treatment by endoscopy or by computed tomography, or by observing the subject's symptoms and duration of symptoms.

In some embodiments, the methods include surgically removing any nasal polyps present in the subject and/or performing sinus surgery.

In some embodiments, the methods include administering one or more corticosteroids and/or one or more antibiotics.

In some embodiments, the corticosteroid is selected from dexamethasone, prednisone, prednisolone, triamcinolone, cortisol, budesonide, mometasone, fluticasone, flunisolide, and betamethasone.

In some embodiments, the antibiotic is selected from erythromycin, doxycycline, tetracycline, penicillin, beta-lactam, macrolide, fluoroquinolone, cephalosporin, and sulfonamide.

Also provided herein are kits for treating rhinosinusitis in a subject, said kits comprising components for a plurality of doses of a treatment for rhinosinusitis, wherein each dose comprises: a pharmaceutical composition comprising 5-150 mg verapamil; salts, preferably comprising sodium chloride and a buffering agent, optionally sodium bicarbonate; and a device for delivering a volume of the pharmaceutical composition to the subject's nasal passage and sinuses. In some embodiments, said device delivers the pharmaceutical composition to the subject's nasal passage and sinuses in a liquid form.

In some embodiments, the volume is 100 or 150ml up to 250 or 300 ml or 500 ml. In some embodiments, the volume of saline is 100 to 250 ml

In some embodiments, the salts comprise sufficient sodium chloride to provide a final concentration of 0.8-1%, preferably 0.9 percent sodium chloride, and buffering agent to provide a pH of 4.5 to 7.5.

In some embodiments, each dose further comprises one or both of a corticosteroid and an antibiotic.

In some embodiments, the kit also includes a corticosteroid and/or an antibiotic. In some embodiments, the corticosteroid is selected from dexamethasone, prednisone, prednisolone, triamcinolone, cortisol, budesonide, mometasone, fluticasone, flunisolide, and betamethasone. In some embodiments, the antibiotic is selected from erythromycin, doxycycline, tetracycline, penicillin, beta-lactam, macrolide, fluoroquinolone, cephalosporin, and sulfonamide.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Methods and materials are described herein for use in the present invention; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

Other features and advantages of the invention will be apparent from the following detailed description and figures, and from the claims.

DETAILED DESCRIPTION

P-glycoprotein(P-gp), a membrane efflux pump, is overexpressed in CRSwNP[3][4] and regulates the secretion of Type 2 helper T cell(Th2) polarizing cytokines which promote polypoid inflammation[4], suggesting that P-gp may be a druggable target (see, e.g., WO2014/106021). P-gp is secreted into nasal mucus[5] via epithelial derived exosomes and can be used to predict disease severity and response to P-gp inhibitory therapy (see, e.g., WO2019139901).

Verapamil Hydrochloride(HCl) was one of the first inhibitors of P-gp to be identified. Recently, a double-blind, placebo-controlled, randomized clinical trial using oral Verapamil as a novel P-gp inhibitory therapy for CRSwNP (ClinicalTrials.gov #NCT02454608, IND Exemption# 126356)[6] was completed.

The results found that the efficacy of Verapamil was commensurate with both oral steroids and biologic agents with no significant side effects. However, logistic regression analysis demonstrated that the dose utilized was subtherapeutic in patients with higher body mass indices (BMI) and elevated mucus total P-gp levels. These results indicated that while P-gp inhibition using Verapamil is a promising innovative therapy for CRSwNP, an alternative dosing and delivery method is necessary to achieve higher local concentrations while preventing possible cardiac side effects.

Previous human trials have studied the systemic effects of intranasal Verapamil HCl at both 1mg [7] and 5mg [8] per dose. Neither study demonstrated any significant side effects suggesting that topical intranasal Verapamil can be safely administered to subjects at total residual doses below 5mg. Previous *in vitro* data [9][10] indicated that a minimal local dose of 0.03mg of Verapamil HCl would be required to achieve inhibition of P-gp within the nasal epithelium. However, whether a safe and effective dose could be achieved using high volume nasal irrigation was unknown.

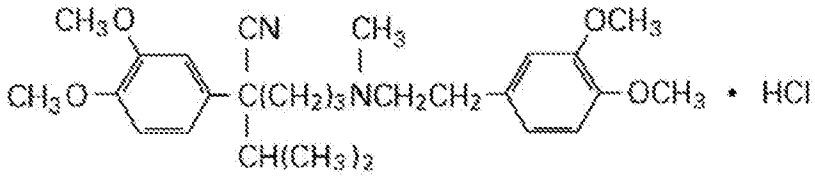
Provided herein are methods of using topical intranasal Verapamil HCl, administered twice daily (BID) at up to the Maximal Tolerated Dose (MTD). The results support the use of high volume, low pressure nasal irrigation to deliver verapamil to subjects with CRSwNP.

Verapamil

Verapamil hydrochloride is a calcium antagonist or slow-channel inhibitor. Verapamil Hydrochloride Injection, USP is a sterile, nonpyrogenic solution containing verapamil hydrochloride 2.5 mg/mL and sodium chloride 8.5 mg/mL in water for injection. The solution contains no bacteriostat or antimicrobial agent. May contain hydrochloric acid for pH adjustment; pH is 4.9 (4.0 to 6.5). The chemical name of Verapamil Hydrochloride, USP is benzeneacetonitrile, α-[3-[{2-(3,4-dimethoxyphenyl)ethyl} methylamino] propyl]-3,4-dimethoxy-α-(1-methylethyl) hydrochloride.

Verapamil hydrochloride is a white or practically white crystalline powder. It is practically odorless and has a bitter taste. It is soluble in water; freely soluble in chloroform; sparingly soluble in alcohol;practically insoluble in ether.

Verapamil has the following structural formula:



Molecular weight: 491.07, Molecular formula: C27H38N2O4 • HCl[12,13]

While Verapamil is a cardioactive drug, it has a long history of use in the treatment of cluster headache in non-cardiac patients. It is considered the first-line prophylactic drug for cluster headache. It is usually well tolerated, although side effects include constipation and occasionally leg edema [14]. The usual starting dose is 80 mg 3 times a day, and the short-acting preparation is usually used. Verapamil has a short half-life (3-7 hours, although half-life may be up to 5-12 hours with chronic dosing) so dosing 3 times a day is necessary. Regular release verapamil tablets are usually used, as the slow release preparations do not seem to be reliable in terms of maintaining blood levels with longer dosing intervals. A concern with verapamil is its effects on atrioventricular conduction. It has been shown that approximately 19% of patients receiving verapamil for cluster headache develop electrocardiogram (EKG) abnormalities, although the great majority of these consist only of prolonged PR intervals, or right bundle branch blocks. However, about 4% can develop complete heart block with junctional rhythms [15]. Because of this, a slow increase in verapamil dosage has been recommended, with the dosage increased from the starting dose of 80 mg 3 times a day by 80 mg every 2 weeks [14] With this regimen, it takes 6 weeks to reach a dose of 480 mg daily. Although some patients will achieve effective prophylaxis at lower doses, patients with cluster headache may require verapamil doses more than this, and these are usually tolerated. Doses up to 640 mg daily are not uncommonly used, and higher doses have been reported to be effective and tolerated. A reasonable escalation regimen in cluster headaches is to start verapamil at 80 mg 3 times a day and to increase the verapamil dosage by 80 mg every week up to a dose of 480 mg daily. Above 480 mg, dosage increases of 80 mg every 2 weeks should be considered to ensure that the dosage is not higher than necessary to control the headaches. Although EKG changes can occur at lower doses, an EKG should certainly be done once a daily dose of 400 mg has been reached, and a

week after each dosage increase above this level. A baseline EKG has also been recommended and periodic follow-up EKGs in patients on maintenance doses of verapamil, as arrhythmias may develop over time on stable verapamil doses [15]. Most patients tolerate even high-dose verapamil well [14]. In a study that reviewed 29 patients with cluster headache who were taking 720 mg or more of verapamil daily, 11 were found to have EKG abnormalities. However, 7 had only bradycardia, and 2 additional patients had only a prolonged PR interval. One patient had a second-degree heart block, and one had a third-degree heart block [16]. In total, 2 patients required discontinuation of verapamil, and one needed a dose reduction. Periodic EKGs are therefore important in patients on verapamil, particularly if they are taking a dose of over 480 mg[14].

Treatment using Verapamil

In some embodiments, a subject having chronic rhinosinusitis (CRS) is identified and treated by administration to the subject an effective amount of verapamil.

CRSwNP is Chronic Rhinosinusitis with Nasal Polyps whereas the term Chronic Rhinosinutis (CRS) encompasses patients with and without nasal polyps. In some embodiments, the present methods are used to treat subjects with CRS without nasal polyps, as some patients with CRS but without polyps still have polyp-like inflammation. The subject having rhinosinusitis may be identified by one of skill in the art based on known methods, e.g., based on detection of the presence of symptoms, by endoscopy, or by computed tomography. The efficacy of the treatment may be monitored by methods known in the art, e.g., by monitoring symptoms, by endoscopy or computed tomography. Improvements of the subject include a better symptom score, e.g. a better SNOT-22 or VAS score; a reduction in inflammation or nasal polyp burden as revealed by endoscopy, e.g. a better Lund-Kennedy score; or a reduction in mucosal thickening or sinus opacification as revealed by computed tomography (CT), e.g. a better Lund-Mackay score. The 22-item Sinonasal Outcomes Test (SNOT-22) is a questionnaire encompassing 22 major symptoms on rhinosinusitis and nasal polyps, and serves as a valuable tool to measure the severity of a subject's symptoms and their impact on health-related quality of life (Quintanilla-Dieck, et al., International Forum of Allergy & Rhinology 2012; 2(6):437-443). The SNOT-22 assessed 12 nasal- and sinus-related symptoms (nasal blockage, loss of

sense of taste and smell; need to blow nose, sneezing, runny nose, cough, postnasal discharge, thick nasal discharge, ear fullness, dizziness, ear pain, and facial pain/pressure) and 10 psychological and behavioral symptoms (difficulty falling asleep, waking up at night, lack of a good night's sleep, waking up tired, fatigue, reduced productivity, reduced concentration, frustrated/restless/irritable, sad, and embarrassed) with participants scoring each symptom on a scale of 0 (absent) to 5 (severe) on average for the last week, for a total score range of 0 to 100. The SNOT-22 score is the mean for the 22 scores (Piccirillo et al., Otolaryngol Head Neck Surg 2002; 126:41–47). The 10-symptom visual analog (VAS) scale is a questionnaire based on the major and minor symptom diagnostic criteria for CRS as described by the American Academy of Otolaryngology–Head and Neck Surgery TFR. The VAS assessed subject-reported severity of each of the following symptoms on average experienced during the prior week: nasal drainage of pus, nasal obstruction/congestion, impaired sense of smell, facial pressure/pain, headache, bad breath, weakness/fatigue, dental pain, ear fullness/pain, and cough (Ryan, et al., Laryngoscope 2011; 121:674–678). The Lund-Kennedy endoscopy scoring system quantifies the pathologic states of the nose and paranasal sinuses as assessed by nasal endoscopy, focusing on the presence of polyps, discharge, edema, scarring or adhesions, and crusting (Ryan, et al., 2011). The Lund Mackay CT scoring system is the most widely used CT grading system for chronic rhinosinusitis. This scoring system consists of a scale of 0-2 dependent on the absence (0), partial (1) or complete (2) opacification of the sinus system and the osteomeatal complex as assessed by CT imaging (Hopkins et al., Otolaryngology–Head and Neck Surgery 2007; 137:555-561).

In the present methods, a subject with chronic rhinosinusitis, e.g., CRSwNP, is treated with the P-gp inhibitor verapamil in an amount sufficient to inhibit P-gp function. The verapamil is administered locally to the subject's nasal passage and sinuses by irrigation with a high volume of saline, e.g., 100 or 150ml up to 250 or 300 ml or 500 ml; in some embodiments, 150 to 240 or 250 ml saline is used. In some embodiments, the amount of drug administered is 5 mg, 10 mg, or 40 mg up to 100 mg, 120 mg or 150 mg, e.g., 5 to 150, 10 to 120 mg, or 40 to 120 mg per dose, and a dose is administered, e.g., once, twice, or three times or more, per day. In some

embodiments, the amount of drug administered is 10 mg, 20 mg, or 80 mg up to 120 mg, 240 mg or 300 mg, e.g., 10 to 300, 20 to 240 mg, or 80 to 240 mg total per day.

In some embodiments, a subject with rhinosinusitis is treated with verapamil in combination with other conventional treatments, e.g., drugs such as corticosteroids and/or antibiotics, to potentiate the effect of treatment. For example, verapamil may be used in combination with a corticosteroid selected from dexamethasone, prednisolone, triamcinolone, cortisol, prednisone, budesonide, mometasone, fluticasone, flunisolide, and betamethasone. In some embodiments, verapamil is used in combination with an antibiotic selected from macrolides, e.g., erythromycin; penicillins, e.g., amoxicillin , beta-lactam, ampicillin; tetracyclines, e.g., doxycycline, tetracycline; sulfonamides, e.g. mafenide, sulfacetamide; fluoroquinolones; and cephalosporins, e.g., ceftaroline fosamil, ceftobiprole. In some embodiments, verapamil is used in combination with a corticosteroid and an antibiotic.

In some embodiments, when a subject with rhinosinusitis has nasal polyps, surgical removal of such nasal polyps and/or sinus surgery can be performed in addition to administration of verapamil to the subject. Thus, a subject with rhinosinusitis may undergo both surgery and treatment with verapamil using the present methods.

Pharmaceutical Compositions, Dosage, Methods of Administration, Kits

The methods of treatment described herein also include the use of pharmaceutical compositions, which include verapamil as an active ingredient. In some embodiments the composition also includes one or more supplementary active compounds incorporated therein, e.g., one or more corticosteroids and/or one or more antibiotics. The corticosteroid can be, e.g., selected from dexamethasone, prednisone, prednisolone, triamcinolone, cortisol, budesonide, mometasone, fluticasone, flunisolide, or betamethasone. The antibiotic can be, e.g., selected from erythromycin, doxycycline, tetracycline, penicillin, beta-lactam, macrolide, fluoroquinolone, cephalosporin, and sulfonamide. Also included are the pharmaceutical compositions themselves.

Pharmaceutical compositions typically include a pharmaceutically acceptable carrier. As used herein the language “pharmaceutically acceptable carrier” includes saline, solvents, dispersion media, coatings, antibacterial and antifungal agents,

isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration.

Pharmaceutical compositions are typically formulated to be compatible with its intended route of administration. The present methods include the use of high volume, low pressure nasal irrigation with saline comprising an effective amount of verapamil.

Methods of formulating suitable pharmaceutical compositions are known in the art, see, e.g., *Remington: The Science and Practice of Pharmacy*, 21st ed., 2005; and the books in the series *Drugs and the Pharmaceutical Sciences: a Series of Textbooks and Monographs* (Dekker, NY).

The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

In some embodiments, a kit for treating rhinosinusitis in a subject is provided. Such a kit comprises a pharmaceutical composition comprising an effective amount of verapamil, optionally a corticosteroid and/or an antibiotic, and a device for delivering the pharmaceutical composition to the subject's nasal passage and sinuses, such as a squeeze bottle. The verapamil (and optional corticosteroid and/or an antibiotic) can be provided in a concentrated form, and the kit can also include sufficient salts to provide an isotonic (normal saline) solution for comfortable nasal irrigation upon addition of water (e.g., distilled or other clean water, not necessarily sterile). In some embodiments, the salts comprise sodium chloride and a buffering agent, e.g., sodium bicarbonate, e.g., sufficient sodium chloride to provide a final concentration of 0.8-1%, e.g., 0.9 percent sodium chloride, and buffering agent to provide a pH of 4.5 to 7.

Each dose of the verapamil (and optional corticosteroid and/or an antibiotic) and salt can be provided in a single container or in multiple individual containers. The containers can be, e.g., a bottle, vial, ampoule, packet or sachet.

The kit can also include one or more viscosity enhancing agents, such as a cellulose polymer or polyethylene glycol (PEG); preservatives; and/or surfactants, which can be incorporated into, e.g. mixed in with, one or more of the verapamil (and optional corticosteroid and/or an antibiotic) and salt. See, e.g., US20180104253.

In addition, the kit can include a bottle, e.g., a reusable bottle, e.g., as known in the art (see also USPN 1603758; 1856811; 3847145; 5649530; 6328718; 6520284; 6736792; 6907879; 8162921; US PGPUB 2006/0276743; 2009/0202665;

2008/0221507; WO 2006/051206; WO 2008/058160; and US2017/0128659, *inter alia.*

EXAMPLES

The invention is further described in the following examples, which do not limit the scope of the invention described in the claims.

Example 1 - Double-blind placebo-controlled randomized clinical trial of verapamil for chronic rhinosinusitis with nasal polyps

We previously undertook a randomized, double-blind, placebo-controlled trial to test the efficacy of low dose oral Verapamil HCl, a known first generation P-gp inhibitor, for the treatment of CRSwNP [6]. While Verapamil is cardioactive, it is considered a first-line prophylactic drug for cluster headache and is well tolerated at 80mg three times a day (TID) by otherwise healthy patients [14]. The findings demonstrated significant efficacy in both our primary and secondary endpoints with no significant side effects. The least squares mean (LSM) change between baseline and week 8 SNOT-22 score was 227.3 (95% CI, 242.56 to 212.05)in the verapamil group and 0.4 (95% CI, 214.85 to 15.66) in the placebo group, resulting in a final LSM difference of 227.7 between groups (95% CI, 249.36 to 26.05; P = .01). Similarly, the final LSM difference in VAS score between groups was 237.97 (95% CI, 260.01 to 215.93; P = .001). The LMS demonstrated a significant difference favoring the verapamil group with an absolute mean difference of25.20 (95% CI, 29.66 to 20.74; P = .02; intraclass correlation coefficient, 0.97). A significant reduction in total LKS was observed in the verapamil group compared with placebo at week 4, with an LSM difference of 22.8 between groups (95% CI, 24.63 to 20.98; P =.003).

However, a linear regression analysis revealed two important relationships between baseline characteristics and efficacy. First, patients with elevated BMI had significantly lower improvements in SNOT-22(p=0.01). This is consistent with the use of a low dose of a relatively low potency inhibitor. The second is that patients with the highest total mucus P-gp levels experienced less benefit (p=0.01). This suggested that the mechanism of Verapamil is acting through P-gp inhibition and that patients with greater expression may need higher concentrations to achieve adequate pump suppression. While Verapamil HCl has significant potential for the treatment of

CRSwNP through P-gp inhibition, higher doses must be achieved to extend the effect to patients with elevated BMIs and the highest levels of P-gp expression. As increasing oral dosing could result in cardiac side effects, topical delivery represents a promising alternative.

Example 2: Phase Ib Clinical Trial of Topical Verapamil HCl for Chronic Rhinosinusitis with Nasal Polyps

This study evaluated the safety and tolerability of nasal delivery of Verapamil using a high volume, low pressure irrigation method. The phase IB study consisted of an accelerated titration, intrapatient dose escalation cohort, with double-dose step design. The initial single patient cohort will began using 10mg Verapamil HCL dissolved in an irrigation bottle containing 240mL buffered saline for nasal use (NeilMed Pharmaceuticals Inc, Santa Rosa, CA) BID for 1 week. Using this method it has been established that 97% of the irrigation volume functions as a carrier which is immediately lost through the nostrils and mouth yielding an approximately effective 3% residual dose of 0.3mg which is retained within the nasal cavity[9]. The first dose was administered in the clinic with EKG and hemodynamic monitoring. Patients were instructed on the how to properly perform the irrigation using a pre-recorded video demonstration. If no first-course dose limiting toxicity (DLT, defined by the development of 2nd or 3rd degree heart block) was noted then patients were instructed to continue taking the current Verapamil rinse dose BID for 1 week. Dose escalation was planned to occur weekly in the absence of a single, any course, DLT or a second, any course, intermediate toxicity (IT, defined by a heart rate of <50, an asymptomatic BP reduction >30% from baseline or systolic BP <90mmHg, an asymptomatic MAP reduction >30% from baseline or MAP<55, an asymptomatic diastolic BP reduction >30% from baseline, and a Meltzer Compliance Grade >4[60]). Each escalation represented a doubling of the residual dose 0.3-2.4mg. At that point the residual dose escalated in 0.6mg residual intervals for the rest of the trial up to a maximum of 3.6mg total residual dose. These doses were derived from the pharmacokinetic analysis of our oral Verapamil trial results. If a single, any course, DLT or second, any course, IT occurs, two additional patients were planned to be recruited at that identified dose and Phase IB would revert to a standard 3+3 design. If any patient un-enrolled during dose escalation they were to be replaced to maintain 3 patient cohorts. The maximal administered dose (MAD) was considered the

immediate preceding dose at which at least 2 DLTs or 4 ITs occurred or the predetermined MTD.

At the conclusion of the study, 8 patients signed consent. These 8 patients included 5 males and 3 females age 18-60, 7 Caucasian (4 M and 3 F) and 1 African-American (1 M). 1 female subject and 5 male subjects completed the study. 5 Caucasian, 1 African-American. The other 2 female subjects were found to be ineligible. Regarding the primary outcome measure, the MAD/MTD was determined to be 120mg IV topical verapamil BID in 240cc buffered normal saline with 0% dose limiting, intermediate, or mild toxicities at the MAD/MTD. Regarding adverse events 1 patient had a transient low heart rate during escalation which resolved at higher doses and 1 patient reported headache.

ARM 2: Phase 2

The Phase II study is an open label safety and efficacy expansion cohort using the MTD determined in the Phase IB arm. A total of 20 patients are administered the MTD of topical Verapamil HCl in a 240mL buffered saline nasal rinse for 4 weeks BID. This sample size was calculated based on a power analysis derived from the results of our oral Verapamil trial. The first dose is administered in the clinic with EKG and hemodynamic monitoring. Patients are instructed on the how to properly perform the irrigation using a pre-recorded video demonstration. If no first-course DLT occurs then patients continue taking the topical Verapamil dose BID. Patients return for follow-up visits at 1 week and 4 weeks. Subjective and objective outcome measures are collected at each visit.

Statistical Analysis

The proposed sample size of 20 subjects for the Phase II expansion cohort was determined to detect, with an 80% power at a 5% type-1 error rate, a change of 15.9 points on the primary endpoint (ie. SNOT-22 score) between baseline and 4 weeks assuming a standard deviation of 24. This calculation was derived from the established MCID for the SNOT-22 of 8.9[11] and our oral Verapamil trial findings[6]. Analysis of efficacy will be based on an intention-to-treat population that will include all enrolled patients. A mixed-effect model with repeated measures approach will be used to independently analyze the change in the SNOT-22, VAS,

and LKS. Linear regression models will be fitted to examine the interaction effect between baseline characteristics, whole mucus and exosomal P-gp concentrations, mucus and irrigant cytokine concentrations, and treatment on change in SNOT-22 while adjusting for the baseline SNOT-22 score.

Subject Inclusion Criteria

Age 18-80 years old ; Diagnosed with Chronic Rhinosinusitis with Nasal Polyps according to the EPOS 2012 consensus criteria; Post-operative with a Lund-Kennedy Poly score of <4; Baseline SNOT-22 Score ≥ 30

Subject Exclusion Criteria

Patients with the following comorbidities: GI Hypomotility; Heart Failure;Liver Failure; Kidney Disease; Muscular Dystrophy; Pregnant or Nursing Females; Steroid Dependency; Hypertrophic Cardiomyopathy; Any Atrial or Ventricular arrhythmia (ie. Atrial fibrillation, atrial flutter, etc..); Resting Heart Rate less than 60 beats per minute; Baseline Systolic Blood Pressure less than 110 mmHg; Baseline Diastolic Blood Pressure less than 70 mmHg; Baseline Mean Arterial Pressure Less than 60 mmHg; PR interval less than 0.12 seconds

Patients taking the following medications: Aspirin; Beta-blockers; Cimetidine(Tagamet); Clarithromycin(Biaxin); Cyclosporin; Digoxin; Disopyramide(Norpace); Diuretics; Erythromycin; Flecainide; HIV Protease Inhibitors(Indinavir, Nelfinavir, Ritonavir); Quinidine; Lithium; Pioglitazone; Rifampin; St Johns Wort

Patients with cardiac or conduction abnormality picked up by screening EKG

Patients with a Systolic BP <100, Patients with a MAP >65, Patients with a HR <65, Patients with a PR interval >200ms, Post-op patients with surgery within 3 months prior to enrollment.

REFERENCES

1. Chin D, Harvey RJ. Nasal polyposis: an inflammatory condition requiring effective anti-inflammatory treatment. Curr. Opin. Otolaryngol. Head Neck Surg. 2013; 21:23–30.

2. Poetker DM, Jakubowski L a, Lal D, Hwang PH, Wright ED, Smith TL. Oral corticosteroids in the management of adult chronic rhinosinusitis with and

without nasal polyps: an evidence-based review with recommendations. Int. Forum Allergy Rhinol. 2013; 3:104–20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22887970.

3. Bleier BS, Article O. Regional expression of epithelial MDR1/P-glycoprotein in chronic rhinosinusitis with and without nasal polyposis. Int. Forum Allergy Rhinol. 2012; 2:122–5.

4. Bleier BS, Nocera AL, Iqbal H, et al. P-glycoprotein promotes epithelial T helper 2-associated cytokine secretion in chronic sinusitis with nasal polyps. Int. Forum Allergy Rhinol. 2014; 4:488–94.

5. Nocera AL, Meurer AT, Miyake MM, Sadow PM, Han X, Bleier BS. Secreted P-glycoprotein is a noninvasive biomarker of chronic rhinosinusitis. Laryngoscope 2016;

6. Miyake MM, Nocera AL, Levesque P, et al. Double-Blind Placebo-Controlled Randomized Clinical Trial of Verapamil for Chronic Rhinosinusitis with Nasal Polyps. J. Allergy Clin. Immunol. 2017;

7. Secher C, Brofeldt S, Mygind N. Intranasal verapamil in allergen-induced rhinitis. Allergy 1983; 38:565–70.

8. Watling S, Engelhardt J, Kandrotas R, et al. Comparison of intranasal versus intravenous verapamil bioavailability. Int. J. Clin. Pharmacol. Ther. Toxicol. 1993; 31:100–4.

9. Harvey RJ, Debnath N, Srubiski A, Bleier B, Schlosser RJ. Fluid residuals and drug exposure in nasal irrigation. Otolaryngol. - Head Neck Surg. 2009; 141:757–761.

10. Sarangapani R, Teeguarden JG, Gentry PR, Clewell HJ, Barton H a, Bogdanffy MS. Interspecies dose extrapolation for inhaled dimethyl sulfate: a PBPK model-based analysis using nasal cavity N7-methylguanine adducts. Inhal. Toxicol. 2004; 16:593–605.

11. Hopkins C, Gillett S, Slack R. Psychometric validity of the 22-item Sinonasal Outcome Test. Clin. … 2009; :447–454.

12. Verapamil Hydrocholride Injection, USP. Prescribing Information. Hospira, Inc. Lake Forest, IL. Revised March 2010

13. Verapamil Hydrochloride Injection. Safety Data Sheet. Hospira GEHS. Revised June 2, 2014

14. Becker W. Cluster headache: conventional pharmacological management. Headache 2013; 53:1191–6. Available at: doi:10.1111/head.12145.

15. Cohen A, Matharu M, Goadsby P. Electrocardiographic abnormalities in patients with cluster headache on verapamil therapy. Neurology 2007; 69:668–675. Available at: doi:10.1212/01.wnl.0000267319.18123.d3.

16. Lanteri-Minet M, Silhol F, Piano V, Donnet A. Cardiac safety in cluster headache patients using the very high dose of verapamil (≥720 mg/day). J. Headache Pain 2011; 12:173–6. Available at: http://link.springer.com/article/10.1007/s10194-010-0289-x.

17. Kocharyan A, Feldman R, Singleton A, Han X, Bleier BS. P-glycoprotein inhibition promotes prednisone retention in human sinonasal polyp explants. Int. Forum Allergy Rhinol. 2014; 4:734–8.

OTHER EMBODIMENTS

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A method of treating rhinosinusitis in a subject, the method comprising identifying a subject having chronic rhinosinusitis;

administering a composition comprising 5-150 mg verapamil to nasal passages and sinuses of the subject using a high volume, low pressure irrigation with normal saline, wherein the verapamil is administered locally to the subject's nasal passage and sinuses by irrigation with a high volume of saline.

2. The method of claim 1, wherein the subject has chronic rhinosinusitis with nasal polyps.

3. The method of claim 1, wherein the composition is administered one or two times a day, preferably wherein a dose of 10-300 mg/day is administered.

4. The method of claim 1, wherein the volume of saline is 100 or 150ml up to 250 or 300 ml or 500 ml.

5. The method of claim 4, wherein the volume of saline is 150 to 250 ml.

6. The method of claim 1, wherein 20 to 120 mg total verapamil per dose is administered, preferably wherein 40-240 mg verapamil is administered per day.

7. The method of claim 1, wherein the subject having rhinosinusitis was identified by endoscopy.

8. The method of claim 1, wherein the subject having rhinosinusitis was identified by computed tomography.

9. The method of claim 1, wherein the subject having rhinosinusitis was identified by observing the subject's symptoms and duration of symptoms.

10. The method of claim 1, further comprising monitoring the efficacy of the treatment by endoscopy.

11. The method of claim 1, further comprising monitoring the efficacy of the treatment by computed tomography.

12. The method of claim 1, further comprising monitoring the efficacy of the treatment by observing the subject's symptoms and duration of symptoms.

13. The method of claim 1, further comprising surgically removing any nasal polyps present in the subject and/or performing sinus surgery.

14. The method of claim 1, further comprising administering one or more corticosteroids and/or one or more antibiotics.

15. The method of claim 14, wherein the corticosteroid is selected from dexamethasone, prednisone, prednisolone, triamcinolone, cortisol, budesonide, mometasone, fluticasone, flunisolide, and betamethasone.

16. The method of claim 14, wherein the antibiotic is selected from erythromycin, doxycycline, tetracycline, penicillin, beta-lactam, macrolide, fluoroquinolone, cephalosporin, and sulfonamide.

17. A kit for treating rhinosinusitis in a subject, said kit comprising components for a plurality of doses of a treatment for rhinosinusitis, wherein each dose comprises:

a pharmaceutical composition comprising 5-150 mg verapamil;

salts, preferably comprising sodium chloride and a buffering agent, optionally sodium bicarbonate; and

a device for delivering a volume of the pharmaceutical composition to the subject's nasal passage and sinuses.

18. The kit of claim 17, wherein said device delivers the pharmaceutical composition to the subject's nasal passage and sinuses in a liquid form.

19. The kit of claim 17, wherein the volume is 100 or 150ml up to 250 or 300 ml or 500 ml.

20. The kit of claim 19, wherein the volume of saline is 100 to 250 ml

21. The kit of claim 17, wherein the salts comprise sufficient sodium chloride to provide a final concentration of 0.8-1%, preferably 0.9 percent sodium chloride, and buffering agent to provide a pH of 4.5 to 7.5.

22. The kit of claim 17, wherein each dose further comprises one or both of a corticosteroid and an antibiotic.

23. The kit of claim 17, further comprising a corticosteroid and/or an antibiotic.

24. The kit of claim 23, wherein the corticosteroid is selected from dexamethasone, prednisone, prednisolone, triamcinolone, cortisol, budesonide, mometasone, fluticasone, flunisolide, and betamethasone.

25. The kit of claim 23, wherein the antibiotic is selected from erythromycin, doxycycline, tetracycline, penicillin, beta-lactam, macrolide, fluoroquinolone, cephalosporin, and sulfonamide.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US20/24476

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/277, 31/275, 9/08, 47/02; A61P 11/02 (2020.01)

CPC - A61K 31/277, 31/275, 9/0012, 9/0043, 9/08, 47/02; A61P 11/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	CLINICALTRIALS.GOV "Trial of Topical Verapamil in Chronic Rhinosinusitis With Nasal Polyps" NCT03102190, 05 April 2017 (pages 1-9) (retrieved 09 May 2020). Retrieved from the internet at URL: < https://clinicaltrials.gov/ct2/show/NCT03102190>; page 1, brief summary; page 4, arm and intervention/treatment; page 5, inclusion criteria	1-6 --- 7-25
Y	US 2017/0348384 A1 (MASSACHUSETTS EYE AND EAR) 07 December 2017; claims 14 and 17; paragraphs [0008]-[0009], [0011]-[0013], [0016]-[0017], [0092], [0099]	7-25
A	NORTHWESTERN MEDICINE "Nasal Saline Irrigation Instructions" June 2018 (retrieved 11 May 2020). Retrieved from the internet at URL: <file:///U:/Downloads/northwestern-medicine-nasal-saline-irrigation-instructions.pdf>; page 1	1

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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