Protocol Title: Potential for Cortisol Suppression with the Use of High Volume Nasal Mometasone Irrigations in Varying Dosages

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Objective:
To determine incidence of cortisol suppression with the use of high volume nasal Mometasone irrigations in varying dosages.

Study Duration: 1 year

Timeframe of study treatment and participation: 12 – 16 weeks

Inclusion Criteria:

- Age 18+
- Diagnosis of Chronic Rhinosinusitis, with or without nasal polyposis
- History of prior endosopic sinus surgery
    - Must include at least ethmoidectomy with maxillary antrostomy

Exclusion Criteria:

- Exposure to systemic corticosteroids within one month of the date of enrollment in to the study.
- Adrenal insufficiency
- Liver disease
- Use of oral estrogens in women
- Morbid obesity (BMI > 38)
- Concurrent pregnancy
- Use of medications which may alter HPA axis(refer to Drugs that affect HPAA)
- Ciliary dysmotility, cystic fibrosis, sarcoidosis, systemic vasculitis, IgG or IgA deficiency, known pituitary or adrenal disease

Intervention:

1. Pre study variables to be collected
    a. Demographic data including MRN, Name, Age, Sex, BMI
    b. Laboratory data including AM cortisol level and pregnancy testing.
    c. Imaging data
    d. Pertinent medical history related to sinus disease

e. Concomitant medication H/o (Avoid drug interactions – refer to the drug interactions section)
f. Hx of arenal insufficiency and liver disease
g. Asthma history
h. Allergy history
i. ASA intolerance
j. Smoking history
k. Lund-Mackay radiographic score
l. Modified Lund-Mackay endoscopic score
    i. Only if able to be used preoperative. May be a strictly postoperative scoring system.
m. Presence/absence of polyps

2. Enrolled pts will be randomized on first come first serve into one of the three Mometasone irrigation groups (15 subjects in each dose study group)
    a. 1mg, 2mg, 4mg BID nasal sinus irrigation dose (see pharmacokinetic calculations in rationale)
3. Patients will be followed and treated as standard care. No additional patient visits will be required as part of the research protocol.
4. AM cortisol testing will be performed at 12 – 16 weeks after 12 weeks of continuous topical irrigation use
    a. Testing will be performed between 6-10 am
        i. This is the standard in the literature
        ii. RUMC lab hours 7am-5:30pm M-F
    b. If patient requires steroid burst for medical reasons, testing schedule will be delayed 1 month from oral steroid use
5. Subjects with abnormal blood cortisol levels after 12 weeks of continuous topical irrigation will have a repeat blood cortisol level tested and if abnormal will be follow up with an Endocrinologist.

Drugs which affect the HPAA:

- Mifepristone
- Cyproheptadine, ketanserin, ritanserin, metergoline
- Bromocriptine, cabergoline
- Reserpine
- Valproic acid
- Octreotide, lanreotide, pasireotide
- Pioglitazone, rosiglitazone
- Metyrapone, Trilostane, mitotane, aminoglutethimide, ketoconazole, fluconazole, etomidate
- Sertraline, citalopram, Trazodone
- Clonidine
- MDMA, cocaine, amphetamine
- Methadone, buprenorphine, naltrexone

- Olanzapine, quetiapine, imipramine, desimipramine, clomipramine, mirtazapine
- Medroxyprogresterone, megestrol, Raloxifene

Drug Interactions

- Avoid combination with Desmopressin
- Monitor therapy while on

A. CYP3A4 Inhibitors (Strong) Interacting Members Atazanavir; Boceprevir; Clarithromycin; Cobicistat; Darunavir; Idelalisib; Indinavir; Itraconazole; Ketoconazole (Systemic); Lopinavir; MiFEPRIStone; Nefazodone; Nelfinavir; Ombitasvir, Paritaprevir, and Ritonavir; Ombitasvir, Paritaprevir, Ritonavir, and Dasabuvir; Posaconazole; Ritonavir; Saquinavir; Telaprevir; Telithromycin; Voriconazole
B. Ceritinib.
C. Ritodrine

Mometasone Study Rationale

The addition of budesonide 0.5 mg/2 ml respules to nasal irrigations has become common practice in the treatment of chronic rhinosinusitis[1-2]. The dose of budesonide 0.5 mg/2 ml was chosen as a result of convenience, as budesonide respules are commercially available as an inhalation in the treatment of asthma. Mometasone is an alternative to budesonide with improved pharmacokinetics resulting in increased local efficacy and lower systemic absorption, however, data is limited in its use as a topical irrigation formulation.

There is relevant literature available discussing the pharmacokinetic profile of budesonide and mometasone used intranasally. Following intranasal administration a drug may enter systemic circulation through direct local absorption in the nasal mucosa or oral absorption of any swallowed medication[3]. The intranasal bioavailability of budesonide and mometasone through nasal mucosa have been measured at 34% and <0.1% respectively[4]. If a drug enters systemic circulation through the nasal mucosa, the medication is subject to plasma protein binding. When a medication is protein bound it is not bioactive and thus reduces the potential for systemic adverse effects. Approximately 85-90% of budesonide is bound to plasma proteins after entering systemic circulation[5]. Alternatively, mometasone is 99% protein bound at clinically relevant concentrations[6]. Therefore, budesonide is bioactive at 10-15 times the concentration of mometasone in the serum due to plasma protein binding.

A portion of the drug may also be cleared from the sinuses into the throat and swallowed, making it available for gastrointestinal absorption. Medications absorbed through the gastrointestinal tract are subject to first pass hepatic metabolism which largely determines the amount of medication which reaches systemic circulation. Approximately 90% of swallowed budesonide is metabolized by the liver during first

pass metabolism[7]. On the other hand, when mometasone is swallowed and undergoes first pass metabolism, 99% of the drug is eliminated leaving only 1% of the drug to enter the circulation[7].

A desired pharmacokinetic property of intranasal steroids is high lipophilicity. Higher lipophilicity leads to increased intranasal absorption as well as prolonged retention in the nasal tissue[3]. Longer retention of the steroid in nasal tissue results in increased exposure to the glucocorticoid receptor[8]. The relative lipophilicity of budesonide and mometasone are 3,980 and 50,000 respectively[6,9]. Thus, mometasone has twelve times higher lipophilicity than budesonide.

In order to determine the proper dose of mometasone, it is important to take into account the volume of nasal irrigation that will remain in the sinus cavity. In patients who have undergone endoscopic sinus surgery, after performing a nasal irrigation with a 240 ml saline filled Neilmed bottle, the result is 1.2% to 5% of the solution remaining in the sinuses[10]. Therefore, the maximum amount of fluid left in the sinuses after a 240 ml nasal irrigation is 5% of the total volume or 12 ml. Applying this data one may estimate the maximum absorption of mometasone added to a 240 ml saline filled Neilmed bottle for irrigation.

- Mometasone 1 mg capsule dissolved in 240 mg
  - 1 mg/ 240 ml = 0.00416 mg/ml or 4.16 mcg/ml
    - Max volume that can be retained in sinuses is 12 ml
    - 12 ml x 4.16 mcg/ml = 50 mcg
    - Medication dosed twice daily, therefore total daily dose = 100 mcg
- Mometasone 2 mg capsule dissolved in 240 mg
  - 2 mg/ 240 ml = 0.00833 mg/ml or 8.33 mcg/ml
    - Max volume that can be retained in sinuses is 12 ml
    - 12 ml x 8.33 mcg/ml = 100 mcg
    - Medication dosed twice daily, therefore total daily dose = 200 mcg
- Mometasone 4 mg capsule dissolved in 240 mg
  - 4 mg/ 240 ml = 0.0166 mg/ml or 16.6 mcg/ml
    - Max volume that can be retained in sinuses is 12 ml
    - 12 ml x 16.6 mcg/ml = 200 mcg
    - Medication dosed twice daily, therefore total daily dose = 400 mcg

Mometasone nasal spray is currently FDA approved at a dose of 2 sprays (100 mcg) in each nostril twice daily for the treatment of nasal polyps. Total daily dose is 400 mcg[11]. Therefore even at a dose of mometasone 4 mg used in a 240 ml nasal irrigation, the total daily dose is equivalent to that of the mometasone nasal spray.

There is current relevant data to assess the safety of mometasone administered intranasally. A review of 20 clinical trials with more than 6,000 patients worldwide at doses up to 20 times the recommended daily dose found no detectable effect of mometasone on the hypothalamic-pituitary-adrenal axis (HPA)[12]. Additionally, mometasone at high doses, did not cause atrophy to the nasal mucosa[12]. Intranasal mometasone at a dose of 1600 mcg, which is 4 times the recommended dose administered daily to human volunteers for 29 days showed no incidence of adverse

effects[11]. The effects of oral mometasone on HPA axis function has also been studied. Oral mometasone was administered at doses of 2, 4, and 8 mg to 24 healthy male volunteers with no significant change in plasma or urinary cortisol from placebo[13].

References:

1. Smith, K. A., French, G., Mechor, B., & Rudmik, L. (2016, March). Safety of long-term high-volume sinonasal budesonide irrigations for chronic rhinosinusitis. In *International forum of allergy & rhinology* (Vol. 6, No. 3, pp. 228-232).
2. Soudry, E., Wang, J., Vaezeafshar, R., Katznelson, L., & Hwang, P. H. (2016, June). Safety analysis of long-term budesonide nasal irrigations in patients with chronic rhinosinusitis post endoscopic sinus surgery. In *International forum of allergy & rhinology* (Vol. 6, No. 6, pp. 568-572).
3. Derendorf, H., & Meltzer, E. O. (2008). Molecular and clinical pharmacology of intranasal corticosteroids: clinical and therapeutic implications. *Allergy*, *63*(10), 1292-1300.
4. Sastre, J., & Mosges, R. (2012). 1 Local and Systemic Safety of Intranasal Corticosteroids. *Journal of Investigational Allergology and Clinical Immunology*, *22*(1), 1.
5. Pulmicort(R) [package insert]. Wilmington, DE: AstraZeneca; 2000.
6. Hochhaus, G. (2008). Pharmacokinetic/pharmacodynamic profile of mometasone furoate nasal spray: potential effects on clinical safety and efficacy. *Clinical therapeutics*, *30*(1), 1-13.
7. Lipworth, B. J., & Jackson, C. M. (2000). Safety of inhaled and intranasal corticosteroids. *Drug Safety*, *23*(1), 11-33.
8. Corren, J. (1999). Intranasal corticosteroids for allergic rhinitis: how do different agents compare?. *Journal of allergy and clinical immunology*, *104*(4), s144-s149.
9. Brattsand, R. What factors determine anti-inflammatory activity and selectivity of inhaled steroids? Eur. Respir. Rev. 1997, 7, 356– 361.
10. Harvey, R. J., Debnath, N., Srubiski, A., Bleier, B., & Schlosser, R. J. (2009). Fluid residuals and drug exposure in nasal irrigation. *Otolaryngology—Head and Neck Surgery*, *141*(6), 757-761.
11. Nasonex(R) [package insert]. Whitehouse Station, NJ: Merk & CO.,INC; 1997.
12. Davies, R. J., & Nelson, H. S. (1997). Once-daily mometasone furoate nasal spray: efficacy and safety of a new intranasal glucocorticoid for allergic rhinitis. *Clinical therapeutics*, *19*(1), 27-38.
13. Brannan, M. D., Seiberling, M., Cutler, D. L., Cuss, F. M., & Affrime, M. B. (1996, January). Lack of systemic activity with intranasal mometasone furoate. In *JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY* (Vol. 97, No. 1, pp. 62-62). 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318: MOSBY-YEAR BOOK INC.

Parameter	Budesonide	Mometasone
Systemic bioavailability through nasal mucosa	34%	<0.1%
Drug remaining after first pass metabolism	10%	1%
Plasma protein binding	85-90%	99%
Relative lipophilicity	3980	50,000