Safety of low pH drugs

There are a number intranasal FDA approved drugs in the market that have a low 3.5 pH range. Among them: Desmopressin Nasal Spray Solution, Calcitonin Salmon Nasal Solution for chronic use, PATANASE Nasal Spray. A phase 3 nasal spray with a fixed formulation of antihistamine and streoids (Ryaltris™) at a pH of 3.7 also provided information on the nasal safety and tolerability of chronic therapy. In addition a number of citrus based products such as Gencydo (Welleda) are approved in European countries for the treatment of allergic rhinitis.

The results of this wide based body of information are consistent: the use of low pH in the range of 3.5-3.7 is safe and well tolerated.

- Nasal safety of chronic treatment with low pH (3.5-4.5) nasal calcitonin was explored in a 5 years double blind placebo controlled study that included 1255 women.: During 5 years of daily treatment with this low pH intranasal medication 4.4% of the participants withdrew due to nasal side effects in the treatment group and 3.3% in the placebo group. Events of rhinitis, nasal congestion or sneezing were prevalent in 22% of the chronically treated group that have been treated for at least 3 years vs 15% of the placebo group. 97% percent of the episodes in the treatment group and 91% of the episodes in the placebo group where mild or moderate. [i]

- The effect of low pH on the nasal mucosa was investigated in long term study (olopatadine-mometasone combination nasal spray safety information including placebo at pH 3.7):

  GSP301[ii] is an investigational FDC of the antihistamine olopatadine HCl and the corticosteroid mometasone furoate developed as a single nasal spray for the treatment of seasonal allergic rhinitis symptoms (SAR). The product was tested in short-term (14 days) clinical studies and was found to be well tolerated and provided significant, sustained improvements in SAR symptoms versus placebo[iii] .

A long-term (52 weeks) safety and tolerability study compared GSP301 (formulation pH 3.7) with two placebo formulations of differing pH (low pH 3.7, neutral pH 7.0) in patients with SAR.

This phase III, double-blind, randomized, parallel-group study conducted at 33 USA centers and consisted of 12 visits, with a placebo run-in period and a treatment period.

A total of 601 patients were randomized, and 440 patients completed the study.

The patients were followed using multiple endpoints: TNSS (rhinorrhea, nasal congestion, nasal itching, and sneezing), Physician-assessed Nasal Symptom Scores (PNSS), the Rhinitis Control Assessment Test (RCAT), as well as Rhinoconjunctivitis Quality-of-Life Questionnaire–Standardized Activities (RQLQ[S]).

The investigators report that the majority of the patients had laboratory values, vital signs, and physical examination findings within normal ranges at week 52. The rate of abnormal, clinically significant findings on ENT examinations was low and generally similar across treatment groups There were no abnormal, clinically significant findings on eye examinations in any of the treatment group.

Because the incidence of TEAEs could be influenced by the low pH of GSP301 (pH 3.7), a neutral pH placebo formulation (pH 7.0) was included in the current study to compare AEs and other safety parameters between low and neutral pH formulations. There were no clinically relevant differences between GSP301 and placebo pH 3.7 or placebo pH 7.0 in the incidence of AEs or on any other safety assessments, which suggested no potential influence of low pH (pH 3.7). The overall TEAE rates at week 52 were numerically greater in the placebo pH 7.0 group than in the other two low pH treatment groups, although the reasons for this were unclear.

- A similar study aimed at assessing the long term safety of Olopatadine[iv] (Patanase). 648 patients > 12 years of age were included in a randomized, placebo-controlled, double-masked, parallel group study, and were treated with Olopatamide (pH – 3.7) for one year. Epistaxis and bad/bitter taste were more common in patients receiving OLO. These events were mild and transient in

nature. A similar incidence of nasal ulceration, infection and anatomic abnormalities was found in the treatment and placebo groups. Lanier et al concludes that side effects were mild and similar to those observed with other intranasal allergy products.

- Ferrara et al tested the effect of two formulations of citrus based nasal spray at a pH of 3-3.5. The purpose of this study was to create a nasal spray based on lemon pulp extract, in light of the pharmacological properties of lemon, and to evaluate its therapeutic efficacy in different forms of rhinitis. The two formulations contained 6-7% of citric acid (similar to Taffix®). The study included 100 patients that were treated daily and were followed for a month. At the end of the study Nasal scraping was used for collecting samples for cytological evaluation. A control group constituted of ten people was recruited as control and this group was administered with physiological solution (saline solution). The comparison of results obtained before and after the application of nasal spray showed a total reduction of eosinophils granulocytes and mast cells; clinical data were confirmed by improvement of clinical pictures of patients. No adverse events either clinical or adverse histological finding were detected in the nasal mucosa histology[v].

- Dajen and his group[vi] investigated the effect of citrus based nasal solutions (Gencydo) at a pH of 2.3-3.2 after multiple administrations equal to 3-10 times the clinical dose. The group treated and evaluated 18 volunteers to define the effect of the low pH nasal spray on the nasal mucociliary transport time, Neither after intranasal administration of the 1% and 3% Citrus/Cydonia solution nor after placebo solution a prolongation of the perception time was found. They concluded that there is no measurable influence of the test products on the intranasal ciliary function.

- Additionally – a clinical study followed patients who were treated in acidified nasal solution with a pH of 2.5 including nasal endoscopy and found a complete safety profile that was no different from neutral pH[vii].

Summary: multiple long term studies of low pH nasal formulation found that nasal formation at the range used in Taffix is safe and well tolerated.

Safety of HPMC in nasal administration

The safety and functionality of the nasal epithelial cilia is one of the major innate defense mechanisms of the nasal epithelium. While quite a wide range of excipients for nasal drug delivery have been tested and approved for safety, the cellulose polymers and especially HPMC was found to have one of the best safety profile in general and in the protection of the ciliary function (tested as CBF-Ciliary Beat Frequency). One recent study and review of the literature concluded that while HPMC was found to increase the residence time of drugs immersed in its gel- it did not cause any adverse effect on nasal tissue and cells as assessed by alterations in CBF. Upon an increase in polymer concentration, a reduction in CBF was observed when ciliated cells were immersed in the polymer solution, and this decrease returned to baseline when the polymer was removed[viii].

HPMC nasal powder have been in use in Europe and US for close to 20 years (Nasaleze™). This product has been classified as class 1 medical device in Europe and Class 2 medical device by FDA and is approved for sale in Israel. In over 20 years of use over 7 million products were sold with complete safety profile. Close to 30 clinical studies were performed with this product consolidating its safety profile[ix]. The latest safety study published in in April 2020 included rat insufflation study where rats were reated with HPMC powder and then sacrified. Detailed histology studies of the nasal epithelium as well as pharyngeal and respiratory epithelium did not reveal any pathological changes following treatment with HPMC.[x]

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