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ORIGINAL RESEARCH

No Rebound Congestion with Short-Term Use of Oxymetazoline Hydrochloride Nasal Spray Decongestant

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Keywords
Oxymetazoline Hydrochloride, rebound congestion, rhinitis medicamentosa, nasal congestion, rhinitis, decongestant,

Abstract:

Background: The duration of use of oxymetazoline hydrochloride nasal spray is limited due to the risk of rhinitis medicamentosa or rebound congestion. In the United States, there is a 3-day limit on duration of use mandated by the FDA OTC Drug Monograph, whereas in some countries in Europe, the limit is 7 days.

Design: Single center, double-blind, randomized, placebo-controlled, parallel group study in otherwise healthy adults, experiencing nasal congestion.

Objectives: The primary objective of this study was to determine whether rebound congestion occurs after 7 days of treatment with twice daily dosing using 1 of 4 doses of oxymetazoline Hydrochloride nasal spray or saline control. The secondary objective was to determine and compare the nasal decongestant dose response of the 4 dosages of oxymetazoline hydrochloride nasal spray.

Population: One hundred forty-three (143) subjects enrolled in the study, 139 completed the study and 138 included in the efficacy analysis.
Methods: Subjects were randomized to one of five groups:

A. 0.025% Oxymetazoline Hydrochloride, one 50 µL spray per nostril.
B. 0.025% Oxymetazoline Hydrochloride, one 100 µL spray per nostril.
C. 0.05% Oxymetazoline Hydrochloride HCl, two 50 µL sprays per nostril.
D. 0.05% Oxymetazoline Hydrochloride HCl, two 100 µL sprays per nostril.
E. Saline control, two 100 µL sprays per nostril.

All subjects administered the assigned spray twice daily, for seven days. Efficacy evaluations were performed on Days 1, 4, 7, and 8 (12-24 hours post-treatment discontinuation). The degree of nasal congestion (primary efficacy variable) was rated on a 100 mm visual analog scale (VAS_{100mm}).

Results: Comparison of congestion scores (VAS_{100mm}) at baseline with scores at Day 1, 4 and 7 of continuous treatment and at Day 8 (12-16 hours post treatment discontinuation) showed lack of subjective rebound congestion at each timepoint. The mean AUCs (difference in baseline congestion score) for the two highest doses of oxymetazoline hydrochloride (0.05%, 50 µL and 100 µL) were significantly greater than that of saline, whereas the mean AUCs for the two lowest doses (0.025% 50 µL and 100 µL) were not, indicating a dose response effect.

Conclusion: Patients did not experience rebound congestion after using oxymetazoline hydrochloride at any of the evaluated doses, with twice daily application, for seven consecutive days and 12-24 hours following treatment discontinuation. There was a trend towards a dose response effect for oxymetazoline hydrochloride nasal spray.

Introduction

Oxymetazoline hydrochloride is an active ingredient found in topical nasal decongestant. The mechanism of action is thought to be due to the stimulation of the peripheral α-adrenergic receptors of the vascular smooth muscles, leading to blood vessel constriction, with little or no action on β-adrenergic receptors [1]. Oxymetazoline hydrochloride is in the class of long-acting topical nasal decongestants, providing efficacy for up to 12 hours [2] The effect of oxymetazoline hydrochloride is rapid, with nasal decongestion reported to be within a few minutes of administration [3]. Its efficacy as a nasal decongestant has been well established, based on an extensive number of clinical study publications and has been successfully marketed as a nasal decongestant in many countries across the world.

Topical nasal decongestants are marketed in the Over the Counter (OTC) medication setting to temporarily relieve symptoms of nasal congestion due to the common cold and / or allergic rhinitis. Common Colds are reported to be one of the top three diagnoses in the outpatient setting and the most common acute illness in the United States, with the average adult experiencing 2 to 4 colds per year [4]. Similarly, allergic rhinitis is one of the most prevalent chronic conditions worldwide. The World Allergy Organization (WAO) estimates the global prevalence of nasal allergies to range between 10-40% [5].

Despite the benefits of topical nasal decongestant medications, the risk of rebound congestion remains one of the reasons to limit their use. The terms “rebound congestion”, “rebound effect” and “rhinitis medicamentosa” have been used interchangeably in literature, to describe the worsening of nasal congestion for which a topical nasal decongestant was initially prescribed for, during repeated use or after stopping treatment [6,7]. This is a class risk of topical nasal decongestants and does not apply to only oxymetazoline hydrochloride. The incidence of rebound congestion is reported to range from 1% to 6.7% from retrospective studies [8,9]. The pathophysiology of rebound congestion has not yet been fully elucidated. Ischemia of the nasal mucosa due to vasoconstriction of submucosal arterioles resulting from intense stimulation of alpha-2 adrenergic receptors is one hypothesis that has been proposed. The other is the downregulation of alpha-2 adrenergic receptors due to repeated stimulation by nasal decongestants [10].

The clinical onset of rebound congestion is also not clearly defined. Most well-designed studies have reported no evidence of rebound congestion after 10-day treatment with oxymetazoline hydrochloride [11] and even up to 2 to 4 weeks of continuous use [12 ,13, 14]. To limit the risk of rebound congestion associated with use of topical nasal decongestants in the OTC setting, Health Authorities around the world have mandated a limit on the duration of use. In the Unites States, there is a 3-day limit mandated by the FDA over the counter (OTC) Drug Monograph [15] whereas many countries in Europe have a 7-day limit of use.

Given the importance of topical nasal decongestants in the management of nasal congestion, it is important to investigate on the onset of rebound congestion with the use of oxymetazoline hydrochloride to establish the appropriate duration of use to inform evidence-based recommendation practices. The objective of this study was to determine whether rebound congestion occurs after seven days of continuous treatment with twice daily dosing of oxymetazoline hydrochloride nasal decongestant spray.

Supplementary information The online version of this article (https://doi.org/10.52845/CMRO/2022/5-12-4) contains supplementary material, which is available to authorized users.

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Material and Methods:

This was a single center, double-blind, randomized, placebo-controlled, parallel group study conducted in a clinical site in New Jersey, United States between May, and July 1993. The study was approved by an Institutional Review Board and conducted in accordance with FDA regulations (21 CFR 50) and good clinical practice (GCP) guidelines.

Patients

Inclusion Criteria:

- Individuals 18 to 65 years of age.
- Individuals experiencing nasal congestion of at least 30mm (both nostrils) on a 100mm visual analog congestion scale (VAS_{100mm}) but otherwise healthy. At least 70% of subjects had congestion due to allergic rhinitis. The other 30% of subjects had non-allergic rhinitis.

Exclusion Criteria:

- Females who were pregnant, planning on becoming pregnant or nursing a child.
- Individuals with a history of allergic reactions or hypersensitivity to oxymetazoline hydrochloride, pseudoephedrine or any topical or oral decongestant.
- Individuals who had a diagnosis of hypertension or with baseline diastolic blood pressure > 90 mmHg; significant heart disease; diabetes or thyroid disease.
- Individuals who had used a nasal decongestant within seven days prior to the study or oral antihistamine within the past 48 hours, nasally administered corticosteroids or cromolyn sodium within the past two weeks or systemic corticosteroids within the past four weeks.
- Individuals who were taking any medications which the investigators believed would have interfered with interpretation of results; chronic users of nasal decongestants; users of cocaine or any drug which would have interfered with normal nasal function.
- Individuals with conditions, which in the opinion of the investigator would place the subject at increased risk or interfere with interpretation of results (such as gross nasal septal deviations, nasal polyps or any other nasal pathology, and individuals who were using an oral decongestant.)

Experimental Design and Evaluations

Subjects who met all selection criteria were randomized to one of five treatment groups:

- Group A: 0.025% Oxymetazoline Hydrochloride (one 50 µL spray per nostril)
- Group B: 0.025% Oxymetazoline Hydrochloride (one 100 µL spray per nostril)
- Group C: 0.05% Oxymetazoline Hydrochloride (two 50 µL sprays per nostril)
- Group D: 0.05% Oxymetazoline Hydrochloride (two 100 µL sprays per nostril)
- Group E: Saline control (two 100 µL sprays per nostril)

Study objective was to determine whether rebound occurs after seven days of treatment with a twice daily dosing schedule using 1 of the 4 doses of oxymetazoline hydrochloride or saline control. Efficacy evaluations were performed on Days 1, 4, 7, and 8 (12-16 hours post-treatment discontinuation) on a 100 mm visual analog scale (VAS_{100mm}). Subjects also rated their level of congestion on Day 8 compared to their initial level using a verbal scale. Subjects in all groups administered the assigned spray twice daily for seven days and were instructed to follow the labeled instructions of use. No concomitant allergic rhinitis medications were allowed during the duration of the study.

After administering the first dose (Dose 1) on Day 1, subjects remained on site and recorded the time that they first noticed relief from nasal congestion. Relief was defined as noticeably easier breathing. Approximately 1 hour after Dose 1, nasal congestion was rated on a Visual Analog Scale ($VAS_{100\ mm}$) and any other symptoms were rated on a Verbal Scale (0=none to 4=severe). Upon completion of the 1-hour evaluations, subjects were issued a diary and instructed to return to the facility in 8-10 hours and 12 hours following Dose 1. Upon return, diaries were collected, nasal congestion and other symptoms were evaluated as before. For all the on-site evaluations, subjects were in a room that was either non-air-conditioned or had a window open, allowing outside air to enter. Smoking and drinking of coffee or tea were not allowed during this period. Subjects were discharged after Dose 1 evaluations and administration of the second dose (Dose 2). Completion of post Dose 2 congestion evaluations and subsequent daily dosing were done off- site, until return on Days 4 and 7.

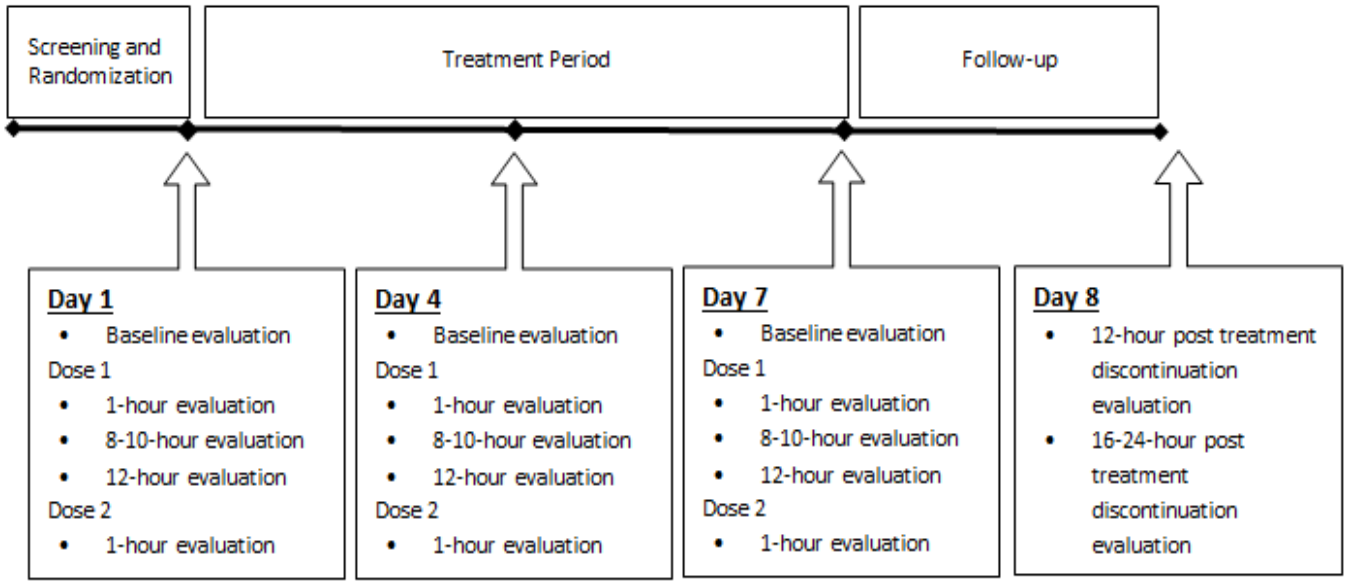

Figure 1: Design Overview

On Days 4 and 7, subjects returned to the site and evaluated baseline nasal congestion and other symptoms, prior to the first daily dosing. They also completed dosing and post dosing evaluations as described on Day 1.

On Day 8, subjects returned to the site approximately 12 hours after their last dose on Day 7. Twelve (12) hours and 16 to 24-hour post treatment discontinuation evaluations were completed. Additionally, subjects answered questions comparing their current level of congestion to their normal level of congestion experienced at baseline.

Statistical analysis

The primary outcome was the occurrence of rebound congestion based on comparison of nasal congestion score at baseline (Day 1) versus Day 4 and 7 baseline using Analysis of Variance (ANOVA). Further, to be certain that rebound congestion did not occur following the discontinuation of treatment, ANOVA of comparative congestion scores for Day 8 (12 hours after last dose, 16-24 hours after last dose) was performed. Secondary outcomes of interest were dose response (mean AUC of change from baseline congestion scores), and number of subjects experiencing relief of nasal congestion within or after 1 hour on Day 1; Day 4; and Day 7.

Results:

Demographics

One hundred forty-three (143) subjects were enrolled in the study. Of the one hundred forty-three (143) subjects enrolled in the study one hundred thirty-eight (138) were included in the efficacy analysis due to one (1) subject discontinuing for failure to keep visits, two (2) subjects discontinuing for non-compliance, and the other two (2) subjects discontinuing due to adverse events. Of the one hundred thirty-eight (138) subjects, majority of them were females, one hundred and three (103) and the rest of them were males, thirty-five (35). Ages of subjects ranged from eighteen to sixty-five years (table 1), with a mean age of 41.5 years.

Table 1: Demographic Data for the Efficacy Population

	Group A 0.025%, 50 µL	Group B 0.025%, 100 µL	Group C 0.05%, 50 µL	Group D 0.05%, 100 µL	Group E Saline	Total
Sex						
Male	7	8	9	4	7	35
Female	21	17	19	25	21	103
Age						
Mean	35.6	37.0	36.5	34.6	37.8	41.5
Range	18-63	19-65	19-65	18-62	19-65	18-65

Rebound Congestion Assessment

Comparison of congestion scores (VAS_{100mm}) at each assessment time point with congestion scores at baseline shows a lack of subjective rebound congestion effect. Table 2 below, displays the mean visual analog congestion score measurements at each time point for each group. Additionally, the Day 8 (12-to-16-hour post treatment discontinuation) congestion scores did not rise above Day 7 (last treatment day) baseline, also indicating a lack of subjective rebound congestion effect following withdrawal of treatment.

Table 2: Visual Analogue Congestion Scores (VAS_{100mm}) Both nostrils

Assessment Timepoint	Visual Analogue Congestion Scores (VAS_{100mm})				
	Group A 0.025%, 50 µL	**Group B 0.025%, 100 µL**	**Group C 0.05%, 50 µL**	**Group D 0.05%, 100 µL**	**Group E Saline**
Baseline	58.1	60.1	57.1	53.2	53.3
Day 1, Dose 1 (1-hour score)	35.7	38.8	28.4	23.9	35.2
Day 1, Dose 1 (8-10 hour score)	34.8	33.6	32.1	26.8	38.0
Day 1, Dose 1 (12-hour score)	45.0	45.5	43.7	42.6	50.0
Day 1, Dose 2 (1-hour score)	31.5	34.7	26.1	21.7	36.2
Day 4 Baseline	53.2	47.5	43.1	41.5	50.1
Day 4, Dose 1 (1-hour score)	27.7	25.4	25.1	22.2	37.1
Day 4, Dose 1 (8-10 hour score)	36.7	30.3	31.5	27.9	47.0
Day 4, Dose 1 (12-hour score)	49.1	45.0	34.9	41.0	49.8
Day 4, Dose 2 (1-hour score)	33.0	30.2	23.9	23.7	41.9
Day 7 Baseline	46.5	47.9	38.5	39.6	46.5
Day 7, Dose 1 (1-hour score)	26.6	34.5	23.5	21.0	36.0
Day 7, Dose 1 (8-10 hour score)	32.5	35.0	27.5	31.1	37.4
*Day 7, Dose 1 (12-hour score)	44.0	43.6	36.0	37.3	40.3
*Day 7, Dose 2 (1-hour score)	26.9	30.3	22.7	18.4	33.5
Day 8 (12-hour post treatment discontinuation)	41.5	40.8	33.5	31.7	40.8
Day 8 (16-hour post treatment discontinuation	37.0	33.8	33.5	30.7	38.2
*Last treatment day Treatment was administered twice per day across all groups VAS (100mm): The lower the number the better the congestion relief					

Table 3: General comparative congestion scores assessment on Day 8

	Group A 0.025%, 50 µL	**Group B 0.025%, 100 µL**	**Group C 0.05%, 50 µL**	**Group D 0.05%, 100 µL**	**Group E Saline**
8-12 hours post treatment discontinuation	4.4	4.7	4.6	5.0	4.5
16-24 hours post treatment discontinuation	4.6	4.4	4.4	4.8	4.5
Subjects rated current congestion level as: 1= much more than my normal level. 2=moderately more than my normal level. 3=slightly more than my normal level. 4=about the same as my normal level. 5= slightly less than my normal level. 6 = moderately less than my normal level. 7= much less than my normal level					

Subjects reported their Day 8 congestion levels to be about the same as normal levels. Mean ratings ranging from 4.4 to 5.0 across all treatment groups indicating lack of perceived rebound congestion

Dose Response Efficacy Assessment

The area under the curve for congestion difference scores were computed and the means for each treatment group are provided in table 4. The AUC for the two highest doses of oxymetazoline hydrochloride was significantly greater than saline treatment. There was a trend towards a dose response effect since the two means for the 0.05% groups are higher than those for the 0.025% groups.

Table 4: Mean Area Under the Curve for Congestion Scores (Difference from baseline)

Treatment	Mean AUC
0.025%, 50 µL	6448.3
0.025%, 100 µL	6433.9
0.05%, 50 µL	7038.1*
0.05%, 100 µL	6953.0*
Saline	3969.6
*The means are significantly different from saline group using Dunnett's Test with Alpha=0.05 P-Value treatment effect = 0.032	

Time to Congestion Relief

At every time point of assessment (on Day 1, 4 and 7), majority of subjects perceived congestion relief in 1 hour or less indicating rapid and sustained efficacy over time (Table 5).

Table 5: Number of Subjects Experiencing Relief of Nasal Congestion within or after 1 hour

	0.025%, 50 µL		**0.025%, 100 µL**		**0.05%, 50 µL**		**0.05%, 100 µL**		**Saline**	
	< 1 hr	>1 hr	< 1 hr	>1 hr	< 1 hr	>1 hr	< 1 hr	>1 hr	< 1 hr	>1 hr
Day1	25	3	22	3	26	2	26	3	23	5
Day 4	24	4	21	4	25	3	25	4	23	5
Day 7	22	6	18	7	27	1	27	2	17	11

Safety

Overall, fifty-six (56) adverse events were reported. Thirty-one (31) were possibly product-related (table 6), twenty-five (25) were considered non-product related (See appendix 1). All conditions were resolved during the study except for a sprained ankle for which the subject was undergoing continued medical care.

Two (2) adverse events resulted in discontinuation of subjects from the study. One (1) subject complained of tightness of the chest and stomach with increased anxiety, lethargy, and depression, approximately eight hours after taking the initial dose of study medication. The events resolved without any additional treatment.

Table 6: Possibly Product Related Adverse Events

Description of Event	Number of Events	Action Taken, if any
Headache	13	One dose of Tylenol 100mg-1,000 mg in 4/13 events
Light Headedness	4	
Numbness in both nostrils	2	
Nervousness	2	
Subject experienced fatigue four hours post dose that was relieved after napping for 45 minutes.	1	
Runny nose	1	
Sinus Headache	1	
Dry mouth	1	
Sleeplessness	1	
Bloody discharge from nose	1	
Burning sensation in throat	1	
Increase in congestion	1	
Fatigue	1	
Burning of both nostrils	1	
Total	31	

Discussion:

In this randomized, placebo-controlled trial, continuous 7-day use of oxymetazoline hydrochloride nasal spray did not show subjective evidence of rebound congestion. This was based on comparison of patients' nasal congestion scores at baseline to baselines on Days 1, 4, 7 of treatment and Day 8 following treatment. Additionally, patients considered their congestion, to be somewhat less than normally experienced, indicating a lack of rebound congestion effect, up to 24 hours following treatment discontinuation.

Previously published studies have investigated the effect of continuous use of 0.05% oxymetazoline hydrochloride on rebound congestion. These are: Baroody et al. 2011 [12], Watanable et al. 2003 [14], Graf et al. 1999 [11],Yoo et al. 1997 [13], Morris et al. 1997[16],Graf 1996 [17],and Graf and Juto 1994 [18]. All publications support the findings of this study, reporting no evidence of rebound congestion with short term continuous use of 0.05% oxymetazoline hydrochloride at commonly recommended dosing frequency of 2 times per day, the only outlier is Morris et al. 1997. Notably, other studies have reported no evidence of rebound congestion with up to 28 days of continuous use [12,13,14]. In Morris et al study, evidence of rebound nasal congestion was found following 3 days of oxymetazoline treatment, with baseline NAR within the daily and intermittent oxymetazoline groups being

significantly greater on Day 3 compared to Day 1. The results suggested that other factors may have a congesting action that could have contributed to the rebound congestion observed in the oxymetazoline groups. Nevertheless, this did not diminish the effectiveness of the decongestant action over time. Therefore, considering all above published studies, it is evident that 7 days treatment with topical oxymetazoline 0.05% in healthy subjects was not associated with therapeutic tolerance or rhinitis medicamentosa.

An important distinction, and strength, of the current study in comparison to previously published studies [7,13,14,16,17,18,19,20] is that most were conducted in healthy volunteers. The absorption properties of an inflamed nasal mucosa when treated with a topical decongestant is not the same as a healthy nasal mucosa. Therefore, it makes it difficult to extrapolate results from previously published studies to clinical practice [10]. The nasal mucosa is not subjected to the cytokine environment associated with inflammation and as such, evaluation of the congestion possibly induced by a topical nasal decongestant is consequently biased by the underlying disease [10]. To circumvent this issue, our study was conducted on subjects suffering from nasal congestion due to rhinitis (allergic and non- allergic).

This study had some limitations. Histopathological assessments were not included in this study although these changes have been reported to be a finding in rebound congestion cases. Furthermore, the study does not include an objective measurement of nasal congestion such as acoustic rhinometry, nasal airway resistance (NAR), or peak nasal respiratory inspiratory flow (PNIF). However, nasal congestion is a subjective perception of nasal patency and objective assessments of nasal congestion have not been found to be strongly correlated with subjective assessment [21].

This study adds to the body of evidence pointing to the lack of rebound congestion with short term use of 0.05% oxymetazoline hydrochloride at commonly recommended frequency of use. To the best of our knowledge this is the largest study that evaluated rebound congestion in subjects with rhinitis and not in healthy subjects. Future studies with a focus on assessing use of topical nasal decongestants in patients with rhinitis, to include histopathological assessments such as epithelial lesions are warranted as such studies are scarce.

Conclusion:

Oxymetazoline hydrochloride nasal spray is an effective and fast acting nasal decongestant. The vast majority of adequately designed studies have yielded little to no evidence of rebound congestion when used short term at commonly recommended dosing and frequency. This study provides yet further evidence that oxymetazoline hydrochloride spray can be used for more than 3 days without the risk of rebound congestion.

Transparency:

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Appendix 1: Non-Product Related Adverse Events

Description of Event	Number of Events	Action take, if any
Fatigue	4	
Subject experienced an onset of reddened watery eyes which began five minutes after administration of spray and resolved in 45 minutes	1	
Bloody discharge from nose	1	
Sprained ankle	1	Elevation of affected leg. Ice and analgesics administered
Slight traces of blood when blowing nose	1	
Menstrual cramps	1	1 dose of Aspirin
Drowsiness	1	
Cold symptoms with sore throat	1	
Pain in left sinus cavity	1	
Dizziness	1	
Tingling in scalp	1	
Sore nostril	1	
Nausea	1	
Sore throat	1	
Itchy throat	1	
Sinus headache	1	
Headache	1	Tylenol
Bloody discharge in both nostrils	1	
Migraine headache	1	1 tablet of Midrin
Congestion in lungs bilaterally	1	
Diarrhea	1	2 tablets of Kaopectate
Continuous dry hacking cough	1	
Total	25	

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