Two-Hour Nasal Responses after a Single Dose of Ephedrine Nasal Spray in Healthy Males

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Background: *Ephedrine is often used as nasal decongestant. Yet, the clinical study of intranasal ephedrine is scarce. In addition, the study tools may affect the measurement of the nasal patency. This problem has not been concerned.*
Objective: *To investigate the nasal responses after using a single-dose of calibrated ephedrine nasal spray in Thai healthy male volunteers. The study also compared the differences between two methods of nasal patency measurement.*
Material and Method: *Healthy males (n = 20) were recruited in a randomized, crossover, 2-day study. Each day was studied for anterior rhinomanometry (RN) or peak nasal inspiratory flow (PNIF). On test day, subjects were given ephedrine nasal spray, and measured by the specific tool for two hours. In addition, the visual analogue scale (VAS), cardiovascular (CVS) parameters, and adverse drug reactions were examined.*
Results: *A single-dose ephedrine nasal spray significantly changed the nasal airway resistance (NAR), PNIF, and VAS at 5-minute. The NAR via RN was maximally decreased by 43.74±16.3% at 10-minute and returned to baseline at 90-minute. While, PNIF was maximally increased by 31.20±18.4% at 10-minute and returned to baseline at 60-minute. The nasal responses measured by two methods were significantly different at 5-, 15-, and 45-minute. VAS for nasal patency showed significant increases throughout the study period. CVS effects were negligible. Bitter taste was the most common adverse event reported.*
Conclusion: *Ephedrine nasal spray is a fast-onset, short-acting decongestant. The decongestant effect of the drug varied by study tools. The variations appeared on the degree of nasal response and duration of action. The drug was generally safe.*

Keywords: *Ephedrine, Rhinomanometry, Peak nasal inspiratory flow, Visual analogue scale*

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Ephedrine is often used as a nasal decongestant, but most studies of ephedrine are predominantly in cardiovascular (CVS) field. Studies of nasal responses after intranasal ephedrine are lacking. Little is known regarding its onset of action, time to peak effect, maximal effect, duration of action, and adverse effects.

The objective evaluations of the nasal decongestant effect are commonly included rhinomanometry (RN) and peak nasal inspiratory flow (PNIF). The two methods were compared in several studies[1-3]. However, there is no comparison of the two methods in the presence of an active decongestant that displayed a time-course manner. Such study could elucidate their uses in drug tests.

Therefore, the purposes of the present study included: i) investigations of nasal responses after a single dose of ephedrine nasal spray in healthy males, and ii) comparison of the two objective methods, RN versus PNIF for two hours after ephedrine nasal spray.

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Material and Method

Subjects

Healthy male subjects (age 18 to 35 years old) without apparent or active nasal problems were recruited. Subjects who had these problems were excluded: allergic rhinitis, active sinusitis, active flu, deviated nasal septum, nasal polyp, past history of nasal surgery, and active conjunctivitis. Subjects with asthma, glaucoma, hypertension, and heart disease were also excluded. Subjects were not allowed to take any medications prior to study for two weeks for corticosteroids, three days for oral decongestants, one day for topical decongestants, one week for antihistamines, and two days for topical eye preparation. No coffee or caffeinated beverages was allowed on the experimental day. Informed consent was done. The study protocol was approved by the Ethical Committee of Faculty of Medicine, Chiang Mai University (CMU).

Standardization of ephedrine nasal spray

Ephedrine (0.5% and 1%, purchased from Pharmacy Unit, CMU) was packaged into an empty nasal spray bottle (Nasacort® AQ, purchased from Pharmacy Unit, CMU). To standardize the dose per spray, the filled bottle was weighed on 4-decimal scale (Sartorius BP 61, Germany) before and after each spray. The lost volume per spray was recorded to evaluate spray volume output variation in terms of coefficient of variation (CV), which was a ratio of standard deviation to mean. As the result, a spray volume output had a very low variation (CV = 1.58%, n = 10 sprays). Validation method was preset before commencing the study and was carried out every seven days to ensure the limited variation during the study.

At first, 1% ephedrine was used because this concentration was commonly applied in adults. However, healthy subjects robustly responded below the limit of quantitation by study tool (RN). Therefore, 0.5% ephedrine was used throughout the study. Eventually, one spray volume output was 0.0945±0.0015 mL. As the result, one spray of 0.5% ephedrine contained 0.47 mg active ingredient. It was delivered at one spray per nostril to every subject.

Study protocol

This was a crossover design that had two randomized visits, for RN or PNIF test (48-hour apart). Subjects sat in a quiet room with minimal interference on sympathetic tone. They were acclimatized for 30 minutes before the study. Subjects were screened, and had anthropometric data collected. They were informed consent and demonstrated details about the procedures, including rehearsals of measurements. During study, drinking water was limited to 400 mL with no food/snack allowed. Nasal responses were assessed at -15-, 0-, 5-, 10-, 15-, 30-, 45-, 60-, 90-, 120-minute. At 0-minute, subjects received baseline measurement, and then were given one ephedrine spray per nostril.

Spraying method

After priming the spray, the investigator held spray pump unit firmly with the index and middle finger on the spray tip and thumb on bottom of the bottle. The spray tip was put into one nostril and pointed straight while the subject bent head forward and closed the other nostril with finger. Spray unit was pumped firmly and quickly for a full-stroke actuation with thumb. On counting, subject sniffed the drug gently.

Endpoints

The primary endpoints included 2-hour measurements of nasal airway resistance (NAR) and PNIF against the baseline. The secondary endpoints included NAR versus PNIF at time points, visual analog scale (VAS) on nasal patency, CVS responses, and adverse events reported after drug administration. For CVS responses, heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were recorded. The adverse reactions were asked upon Likert-type questionnaire to rate symptoms on 0 = none, 1 = mild, 2 = moderate, and 3 = severe. The comparisons were mainly against baseline, except NAR versus PNIF in the secondary endpoints.

Anterior rhinomanometry (RN)

Nasal airflow and NAR were measured by Rhinomanometer 300 (ATMOS Medizin Technik, Germany). Subjects sat upright in air-conditioned room. A nasal adapter (Endomed, Thailand) was inserted to occlude one nostril. Subject kept mouth closed and breathed quietly in a fitted mask for several seconds. Nasal airway resistances were obtained at the transnasal pressure of 75 Pascal (Pa) as recommended by a Thai study[1]. The resistance from each nostril was represented as this equation: $R = \Delta P/V^o$. Whereas, R = resistance ($Pa/cm^3/second$), ΔP = transnasal differential pressure (Pa), V^o = nasal airflow ($cm^3/second$)[4]. The NAR from each nostril was converted to total NAR from this equation: $1/NART = 1/NARL+1/NARR$. Whereas, NART, NARL, NARR were NAR of total, left, and right, respectively[5]. NAR shown in the results denoted total NAR ($Pa/cm^3/second$).

Peak nasal inspiratory flow (PNIF)

PNIF was performed via In-Check® nasal (Clement Clark, UK, distributed by Celki Thai). Manufacturer's instructions were followed. In brief, after reset the device to start position, the device was attached firmly on face at horizontal plane. Subject inhaled forcefully through their nose as the mouth closed. The highest value from three readings was used for analysis.

Visual analogue scale (VAS)

The 10-cm VAS in the study was designed to evaluate the nasal patency. On the far left, the mark labeled the least patent feeling, as the most patent feeling on the far right. After given ephedrine nasal spray, subjects rated the nasal patency along time

course. The VAS for analysis was collected on RN test day. VAS was compared against the baseline.

Sample size calculation

There were very few similar studies. One study measured nasal airflow changes after topical ephedrine, the sample size was only eight[6]. The second study was in Thai healthy subjects, it measured parameters at 5-minute after 3% ephedrine[7]. This yielded the calculated sample size of six or more. A correlation study used 24 healthy subjects to compare between tools without the topical decongestant. Thus, the proposed sample size was initially 24. However, the power of the test for major endpoints reached 80% when 20 subjects were included in the present study.

Statistical analysis

One-way ANOVA with repeated measurement was used for comparison in time-course manner. Due to cross-over design, paired t-test was applied for some parameters. The *p*-value <0.05 was significant difference.

Results

Subjects

In the present study, 21 subjects were enrolled. One subject was found on the second visit test day as having nasal congestion. His data were discarded. Twenty subjects completed the two-day study. Subjects had average age, body weight, height, and body mass index of 27.39±5.4 years, 65.30±7.3 kg, 172.95±6.0 cm, and 21.83±2.2 kg/m^2, respectively.

Nasal airway resistance via RN

NAR at baseline (0-minute) was not significantly different from at -15-minute. At 0-minute, the average NAR was 0.20±0.07 Pa/cm^3/second. Compared to 0-minute, NAR significantly decreased at 5- to 60-minute, and gradually returning to baseline at 90-minute (p<0.01 at 5- to 45-minute; p = 0.01 at 60-minute, Fig. 1).

Total nasal airflow at baseline (0-minute) was not significantly different from at -15-minute. At 0-minute, the nasal airflow was 399.00±110.4 cm^3/second. Compared to 0-minute, the nasal airflow increased significantly at 5- to 60-minute (p<0.01) and gradually returning to baseline at 90-minute (Fig. 2).

PNIF

PNIF at baseline (0-minute) was not significantly different from at -15-minute. At 0-minute, the average PNIF was 133.95±21.3 L/minute. Compared to 0-minute, the PNIF significantly increased from 5- to 45-minute (p<0.02 at 5-minute, p<0.01 at 10- to 30-minute, and p<0.02 at 45-minute). It gradually returned to baseline at 60-minute (Fig. 3).

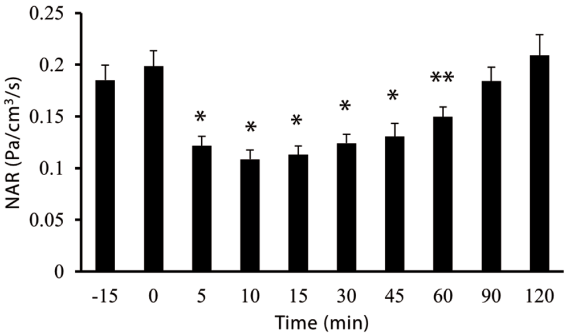

Fig. 1 Nasal airway resistance (NAR, Pa/cm^3/second) measured by rhinomanometry after a single-dose ephedrine nasal spray. Data represented mean with SEM, * p<0.01 vs. 0 minute, ** p = 0.01 vs. 0 minute.

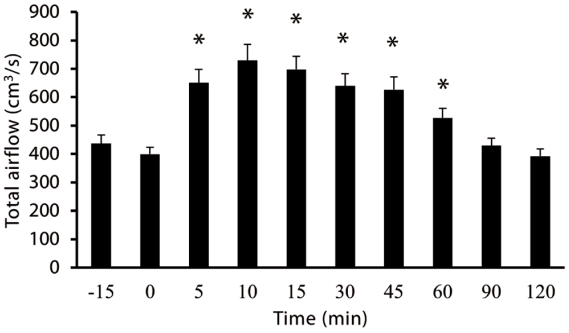

Fig. 2 Total airflow (cm^3/second) measured by rhinomanometry after a single-dose ephedrine nasal spray. Data represented mean with SEM, * p<0.01 vs. 0 minute, ** p = 0.01 vs. 0 minute.

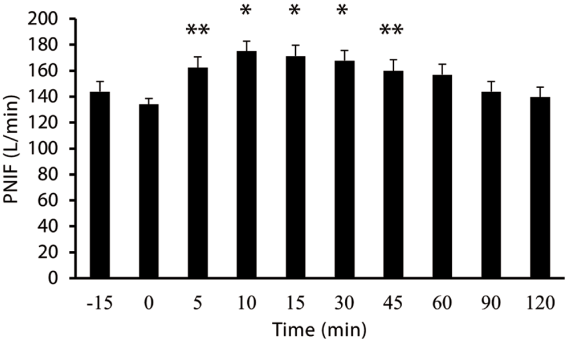

Fig. 3 Peak nasal inspiratory flow (PNIF, L/minute) after a single-dose ephedrine nasal spray. Data represented mean with SEM, * p<0.01 vs. 0 minute, ** p = 0.01 vs. 0 minute.

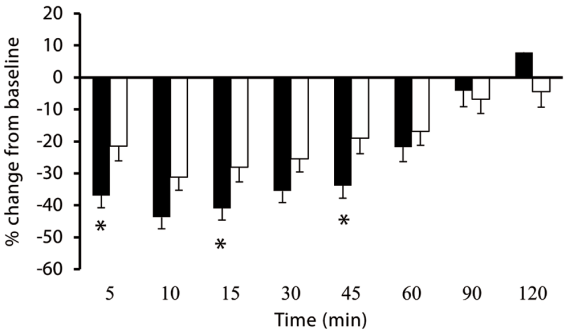

Fig. 4 Comparative response of rhinomanometry (RN, filled bars) and peak nasal inspiratory flow (PNIF, blank bars) after a single-dose ephedrine nasal spray. Note: PNIF was multiplied by -1 to create negative value. The SEM of RN at 120 minute was 7.1 (not shown), * $p<0.05$ vs. comparator.

Onset, time to the peak, and maximal effect

Onset of action measured by PNIF and RN were similarly at 5-minute. Both tools showed the peak effect at 10-minute (Fig. 1, 3). The time to peak effect via RN was 10-minute (n = 12), 15-minute (n = 6), 30-minute (n = 1), and 45-minute (n = 1). Whereas, the time to peak effect via PNIF was 10-minute (n = 9), 30-minute (n = 9), 45-minute (n = 1), and 60-minute (n = 1). The maximal effect at 10-minute was 43.74±16.3% for NAR and 31.20±18.4% for PNIF. Statistical differences between the two tools were observed at 5-, 15-, and 45-minute ($p<0.05$); and all most significant at 10-minute ($p = 0.058$) and 30-minute ($p = 0.057$).

VAS

On RN test day, the VAS was 5.18±1.9 cm at 0-minute. It later increased to 6.70±1.9 cm, 7.30±1.6 cm, 7.64±1.3 cm, 7.55±1.4 cm, 7.51±1.3 cm, 7.31±1.3 cm, 7.00±1.3 cm, and 6.83±1.5 cm, respectively. VAS for nasal patency was significantly increased at every time point ($p<0.05$ vs. 0 minute).

CVS effects after a single-dose ephedrine nasal spray

At 0-minute, SBP and DBP was 117.50±15.1 and 68.60±10.2 mmHg, respectively (Table 1). SBPs were not significantly increased from 0-minute. DBPs significantly increased to 73.90±9.7 mmHg at 90-minute ($p = 0.029$) and to 77.8±10.5 mmHg at 120-minute ($p<0.001$). HR at 0-minute was 76.9±10.3 bpm. HR at other time points were not significantly different from 0-minute.

Adverse events reported

From two visits, total 40 sprays were given to 20 subjects. Thirty-nine events were reported by 16 subjects (80%). The most common events included bitter taste, dry mouth, dry nose, and headache (Table 2). Most adverse events were graded as mild. There were only two moderate events (bitter taste and dry mouth).

Discussion

Ephedrine study is predominant in CVS field. Yet, ephedrine drops have been used for decongestant in Thailand, and available in UK. However, the nasal responses following topical ephedrine have not been studied. From the present study, a single-dose ephedrine nasal spray had the onset before five minutes, peak at

Table 1. Cardiovascular parameters after intranasal ephedrine. Systolic blood pressure, diastolic blood pressure, and heart rate (mean ± SEM, n = 20)

Time (minute)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Heart rate (bpm)
-15	117.2±11.2	71.1±8.3	77.8±10.8
0	117.5±15.1	68.6±10.2	76.9±10.3
5	115.5±13.4	70.0±9.2	78.2±10.4
10	114.9±13.1	68.4±9.1	78.3±10.2
15	115.1±12.2	69.6±8.5	77.7±8.5
30	116.6±14.3	69.4±9.3	75.1±9.4
45	116.1±11.1	71.7±10.3	76.2±8.8
60	115.9±14.2	72.6±8.3	74.3±9.1
90	117.9±13.0	73.9±9.7*	72.6±7.0
120	119.6±12.6	77.8±10.5*	73.5±7.9

* Indicated the statistical significance vs. 0 minute

Table 2. Adverse events reported after a single dose of ephedrine nasal spray (n = 20)

Adverse events	Subjects (%)	Events (% of 40 sprays)
Bitter taste	9 (45)	15 (37.5)
Dry mouth	5 (25)	7 (17.5)
Dry nose	4 (20)	5 (12.5)
Headache	4 (20)	4 (10.0)
Sore throat	2 (10)	2 (5.0)
Stuffy nose	1 (5)	2 (5.0)
Vision changes	1 (5)	1 (2.5)
Cough	1 (5)	1 (2.5)
Palpitation	1 (5)	1 (2.5)
Agitation	1 (5)	1 (2.5)

10-minute, and the duration of action for about 45 to 60 minutes. The maximal decongestant effect was about 43.74±16.3% decrease under RN or 36.20±18.4% increase under PNIF. In application, the present study encouraged physicians to wait for the peak effect of drug (~10 minutes) before doing any procedures. For ephedrine decongestion test, the best value of NAR should be collected at 10- or 15-minute; whereas the best value of PNIF should be obtained at 10- or 30-minute. Others used naphazoline and collected the best value at 5- or 10-minute for analysis[8]. Since intranasal ephedrine could affect co-administered drug absorption in rat model[9]. Results from the present study may give way to the future study regarding nasal drug delivery.

Rather than nasal drops, the present study used metered-dose nasal sprays which were standardized (0.47 mg per spray). Nasal sprays allow drug to deposit anteriorly, while nasal drops allow drug to deposit posteriorly[10]. The narrowest part of the nose is nasal valve, which is located in anterior segment of the nose. It makes the nasal spray a more desirable drug delivery than the nasal drop. However, a deep-seated lesion, e.g., nasal polyp, nasal drops were probably preferable. Fluticasone nasal drops showed superior efficacy to fluticasone nasal sprays in treatment of nasal polyp[11].

The discrepancies between both tools were shown moderately in the degree of nasal response and slightly in the duration of action. Overall, RN was more sensitive than PNIF. Possible reasons included: i) RN measured the resistance, whereas PNIF measured flow rate at its peak, ii) RN measured on 2-decimal scale which detected even small changes, and iii) PNIF was a mechanical device, dependent on human force. Consistently, PNIF was unable to detect the decongestant effect of oral pseudoephedrine when RN could reveal it[3]. Another study compared PNIF with the gold-standard RN in detecting the nasal obstruction. On the ROC analysis, PNIF had 87% sensitivity and 52% specificity[12]. The low specificity of PNIF indicated that many non-obstructive noses were counted as obstructive ones by PNIF. This could explain the lower amplitude and the shorter duration measured by PNIF. On the contrary, a study reported that both tools had similar sensitivity, specificity, and accuracy in detecting nasal obstruction from nasal deformity[2].

A clinical study tested CVS effects after very high dose of intranasal ephedrine. Compared to placebo, 5-mg intranasal ephedrine did not affect SBP, DBP, and HR[13]. So, CVS effects in the present study should be explained by non-pharmacologic causes. Bitter taste was the most reported adverse events (45% of users). This was partly due to healthy subjects with no nasal obstruction, drug then dripped down to the throat.

Limitation of the present study was the small sample size. Hence, PNIF at 60-minute almost had a statistical difference (p = 0.051 vs. 0-minute). In addition, the statistical differences between both tools were almost seen at 10- and 30-minute (p = 0.058 and 0.057, respectively).

In conclusion, a single-dose ephedrine nasal spray was a fast-onset, short-acting decongestant. The decongestant effect of the drug was varied by the study tools. The differences between both tools were appeared clearly on the degree of response and mildly on the duration of action. RN was more sensitive than PNIF in evaluating the decongestant effect. A single-dose ephedrine nasal spray was safe, although, bitter taste was reportedly high.

What is already known on this topic?

Intranasal ephedrine has been used widely, but there has no clinical data of the nasal response. Two ways of evaluations the nasal obstruction are commonly used: RN and PNIF. The two methods are interchangeably used.

What this study adds?

This study revealed the basic pharmacodynamic data of intranasal ephedrine at therapeutic dose. This is very important for future reference. The study also described the difference of both tools in measuring decongestant effects under the time-course manner.

Authors' contributions

Trakarnsilpa C had contributed 50% of the project. Roongapinun S was the principal investigator and corresponding author.

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Potential conflicts of interest

None.

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การตอบสนองของจมูกเป็นเวลา 2 ชั่วโมง หลังจากได้รับยาเอฟฟิดรีนชนิดพ่นจมูกครั้งเดียว

ชีวิน ตระการศิลป์, วรางคณา อาภรณ์ชยานนท์, ณัฐิยา หาญประเสริฐพงษ์, สุปราณี ฟูอนันต์, มาลียา มโนรถ, สุกิจ รุ่งอภินันท์

ภูมิหลัง: *เอฟฟิดรีนเป็นยาที่ใช้บ่อยในการลดคัดจมูกแต่การศึกษาทางคลินิกของยานี้มีน้อยมาก อีกประเด็นคือเครื่องมือในการศึกษาวิจัยอาการคัดจมูกนั้น อาจให้ผลการประเมินที่ไม่เหมือนกัน ปัญหาเรื่องนี้ยังไม่ถูกตระหนัก*

วัตถุประสงค์: *เพื่อศึกษาผลการตอบสนองจากการให้ยาเอฟฟิดรีนครั้งเดียวแบบสเปรย์พ่นจมูกในอาสาสมัครชายไทยสุขภาพดี และเปรียบเทียบความแตกต่างจากการใช้เครื่องมือในการวัดความคัดจมูก*

วัสดุและวิธีการ: *อาสาสมัครเพศชายสุขภาพดีจำนวน 20 คน ได้เข้าการศึกษาวิจัยแบบสุ่มใช้เครื่องมือข้ามกลุ่มในการศึกษาสองวัน โดยแต่ละวันจะทำการวัดด้วยเครื่องมือไรโนมาโนเมตทรี อีกวันจะทำการวัดพีคนาซอลอินสไปราทอรีโฟลว์ การศึกษาจะเริ่มด้วยการให้เอฟฟิดรีนพ่นเข้าทางจมูกหลังจากนั้นจะทำการวัดด้วยเครื่องมือดังกล่าวเป็นเวลา 2 ชั่วโมง รวมทั้งการวัดแบบประเมินความรู้สึกโล่งจมูก วัดค่าทางระบบหัวใจและหลอดเลือด และประเมินผลข้างเคียง*

ผลการศึกษา: *การให้ยาเอฟฟิดรีนพ่นจมูกเพียงครั้งเดียวเปลี่ยนแปลงตัวชี้วัดต่าง ๆ ได้อย่างมีนัยสำคัญตั้งแต่นาทีที่ 5 ค่าความต้านทานในจมูกที่วัดผ่านไรโนมาโนเมตทรีนั้น มีค่าเปลี่ยนแปลงไปสูงสุดร้อยละ 43.74±16.3 ที่เวลา 10 นาที และกลับสู่ค่าตั้งต้นที่เวลา 90 นาที ขณะที่เครื่องมือพีคนาซอลอินสไปราทอรีโฟลว์ มีการเปลี่ยนแปลงสูงสุดร้อยละ 31.20±18.4 ที่นาทีที่ 10 และกลับสู่ค่าตั้งต้นที่เวลา 60 นาที การวัดการตอบสนองของจมูกโดยเครื่องมือทั้งสองชนิดให้ผลที่แตกต่างกันโดยจะเห็นได้ที่เวลาที่นาทีที่ 5, 15 และ 45 นาที ค่าความโล่งจมูกที่ประเมินโดยผู้ป่วยพบว่ามีการเพิ่มขึ้นอย่างมีนัยสำคัญในตลอดการศึกษา ผลของยาต่อระบบหัวใจและหลอดเลือดนั้นมีน้อยมาก อาการขมคอเป็นผลข้างเคียงที่อาสาสมัครรายงานมากที่สุด*

สรุป: *เอฟฟิดรีนที่พ่นทางจมูกออกฤทธิ์ได้เร็วและมีฤทธิ์สั้นในการลดการคัดจมูก โดยที่ฤทธิ์ลดคัดจมูกอาจจะแตกต่างกันไปขึ้นกับเครื่องมือที่ใช้วัด โดยที่ความแปรปรวนนี้จะเห็นได้จากมีระดับการตอบสนองของจมูกที่ต่างกัน และระยะเวลาในการออกฤทธิ์ของยาที่ต่างกัน โดยรวมแล้วยานี้ถือว่ามีความปลอดภัย*