Eur J Clin Pharmacol (1995) 48: 71–75

E. Lunell · L. Molander · M. Andersson

Relative bioavailability of nicotine from a nasal spray in infectious rhinitis and after use of a topical decongestant

Received: 20 May 1994 / Accepted in revised form: 21 October 1994

Abstract The relative bioavailability of nicotine from a nasal spray was assessed in 15 smokers suffering a common cold and rhinitis according to generally accepted criteria. The patients were given a single dose of 2 mg nicotine from the nasal spray with and without concurrent administration of a nasal vasoconstrictor decongestant, xylometazoline, in randomised order. Control session measurements were made in the disease-free state.

Applying strict bioequivalence criteria, we found that common cold/rhinitis slightly reduced the bioavailability of nicotine, both in its rate and extent; the geometric mean of the ratio of C_{max}, AUC and t_{max} were 0.81, 0.93 and 1.36, respectively. The nasal vasoconstrictor, xylometazoline, normalised the extent of the bioavailability of nicotine, but further prolonged the time for absorption to almost twice that measured in the disease-free state, increasing the t_{max} ratio to 1.72.

The results suggest that a minor proportion of people stopping smoking with the help of a nicotine nasal spray may experience a minor reduction in the effect of the spray during common cold/rhinitis. However, the nicotine self-titration behaviour found with most smoking cessation products (except the nicotine patch) will automatically lead to an adjustment of the dosage to achieve the desired effect.

Key words Nicotine, Rhinitis; pharmacokinetics, nasal spray, xylometazoline, drug interaction

E. Lunell (✉) · L. Molander
Pharmacia Research Laboratories, Karl XI gatan 4, S-222 20 Lund, Sweden

E. Lunell
Department of Clinical Pharmacology, University Hospital, Lund, Sweden

M. Andersson
Department of Oto-rhino-laryngology, University Hospital, Lund, Sweden

The nasal cavity is lined with a large area of well vascularized mucosa, which permits the rapid absorption of a number of drugs. Intranasal administration is being explored as an alternative route for drug administration [1].

The development of a nicotine nasal spray primarily stems from experimental work showing rapid absorption of nicotine from nasal snuff [2]. In fact, the plasma nicotine profile after use of a nasal spray is closer to that seen with smoking than any other form of nicotine replacement [3, 4, 5].

For obvious reasons, diseases affecting the nasal mucosa, e.g. inflammatory diseases with nasal obstruction and discharge, may interfere with the absorption of nicotine administered in the nose.

A further complicating factor is the possible treatment of these symptoms with a locally administered vasoconstrictor. As this situation will be faced by many patients using a nicotine nasal spray, it was important to determine the extent to which rhinitis and the concurrent administration of a nasal vasoconstrictor decongestant might affect the bioavailability of intranasal nicotine.

Subjects and methods

Study design

The study had an open, three-way cross-over design. The bioavailability of nicotine from the nasal spray was assessed with and without concurrent treatment with a vasoconstrictor during a confirmed attack of rhinitis and the results were compared with the disease-free state. The sequence between the rhinitis sessions was randomised. The session when the subject was disease-free was performed as soon as possible after the episode of rhinitis.

Subjects

Fifteen healthy smokers, 20 to 40 years of age, participated in the study. They had no history of alcohol abuse or drug dependence. The subjects had to abstain from nicotine for at least 12 h prior to

the drug administration and throughout the entire experimental session. The study was approved by the Ethics Committee of the University of Lund and was conducted in accordance with the Helsinki Declaration. All subjects gave their written consent prior to the start of the study.

Drug administration

A nicotine nasal spray (Nicorette® 10 mg · ml^{-1}) and a nasal spray containing the vasoconstrictor xylometazoline (Otrivin® 1 mg · ml^{-1}) were used. Each spray delivered a solution containing 0.5 mg nicotine in 50 µl and 0.14 mg xylometazoline in 140 µl, respectively. The recommended dose of nicotine nasal spray was one spray into each nasal cavity (i.e. 1 mg), one to two doses per hour and not exceeding 3 doses per hour. To ensure plasma nicotine levels above the limit of quantification for a long enough time period to allow adequate pharmacokinetic calculations, two doses (each of 1 mg) were given with 5 min between each dose.

Before administration the nicotine and decongestant spray bottles were "primed" by spraying five times into the air, in order to demonstrate proper functioning of the devices. To avoid nicotine contamination this was done in a separate room by someone not involved in taking the blood samples.

One spray (0.5 mg nicotine) of nicotine solution was sprayed into each nasal cavity by one of the investigators. The procedure was repeated after 5 min of quiet rest. The nozzle of the spray bottle was inserted parallel to the septum, with its front edge just inside the nasal vestibule. The nozzle was pointed between the frontal wall and the nasal floor.

The subject had to blow his nose before the first dose and to sit upright during treatment. The vasoconstrictor xylometazoline was administered 30 min prior to the nicotine nasal spray. One spray (0.14 mg xylometazoline) was given into each nostril.

Verification of common cold/rhinitis

Common cold/rhinitis was confirmed by fulfillment of Criteria 1 and/or 2 and Criterion, 3 as described below [6].

Criterion 1

A total score of 14 points or more for the following symptoms characteristic of the common cold: sneezing, headache, malaise, chilliness, nasal discharge, nasal obstruction, sore throat, cough graded 0–3 (none, mild, moderate, severe) by the subject and reported in response to active questioning according to a checklist.

Criterion 2

The impression of the subject him/herself that a common cold had developed, with fewer than 14 symptom points.

Criterion 3

The presence both of increased nasal discharge (rhinorrhoea) and swelling (graded 1–3), as assessed by anterior rhinoscopy.

Rhinoscopy assessment

The degree of swelling, nasal discharge and reddening was estimated using a scale of 0–3 points. These scores were not included in the total symptom score.

Concomitant therapy

Oral contraceptives were allowed. There were no restrictions on the use of OTC products, except nasal decongestants, neither before nor during the study. No prescribed medication or drug under investigation was used concomitantly with the study drug.

Blood sampling

Venous blood samples (5 ml) were collected from an antecubital vein into sodium heparinised glass tubes at the following times: 0 (directly prior to administration) and 15, 30, 45, 60, and 90 min and 2, 3, 4, 5, and 6 h after administration of the first dose.

The blood samples were cooled and centrifuged at 4 °C within 30 min and plasma was transferred to cryo-tubes which were kept frozen (–20 °C) pending analysis.

Bioanalysis

Nicotine was determined by capillary gas chromatography after single step liquid-liquid extraction of the plasma sample. It was detected by means of a nitrogen sensitive detector of high selectivity and sensitivity [7]. The precision of the method above the 0.7 ng/ml level of nicotine was better than 11.0 % C.V., and above 4 ng/ml it was better than 6.0 % C.V. The level of quantification was 0.6 ng · ml^{-1}.

Pharmacokinetic calculations

For each administration the following calculations were performed: AUC_{inf} was calculated as AUC_{0-t}, where t denotes the last time point, by the linear trapezoidal method plus the area from t-∞ using the equation

$$\frac{C_t}{k_{el}}$$

The elimination rate constant, k_{el}, was obtained by linear regression of the plasma concentration values of the terminal slope of the logarithmic plasma concentration-time curve. The maximum nicotine plasma concentration (C_{max}) and the time to peak plasma concentration (t_{max}) were determined from the observed plasma concentration-time curve. AUC_{inf} and C_{max} were corrected for baseline nicotine concentration (C_o) as shown below:

$$AUC_{inf} - \frac{C_o}{k_{el}}$$

$$C_{max} - C_o \cdot e^{-k_{el} \cdot t_{max}}$$

Pharmacokinetic interaction

The variables AUC and C_{max} were analysed using ANOVA (least squares means) and after natural logarithm transformation of the variable, while t_{max} was analysed using the Wilcoxon test and rank transformed data.

The conventional methodology of bioequivalence analysis was used to evaluate the effect of common cold/rhinitis and xylometazoline on the pharmacokinetics of intranasally administered nicotine. The following comparisons were made (test/reference): common cold/rhinitis vs normal and rhinitis + xylometazoline vs normal.

Bioequivalence, i.e. lack of interaction, which was assessed both for the rate (C_{max}, t_{max}) and extent (AUC_{inf}), was accepted if the 90 % confidence interval (with error from ANOVA) for the log transformed AUC_{inf}-, C_{max}- and t_{max}-ratios (test/reference) were contained within the interval 0.8–1.25 (AUC_{inf}, C_{max}) and 0.7–1.43 (t_{max}).

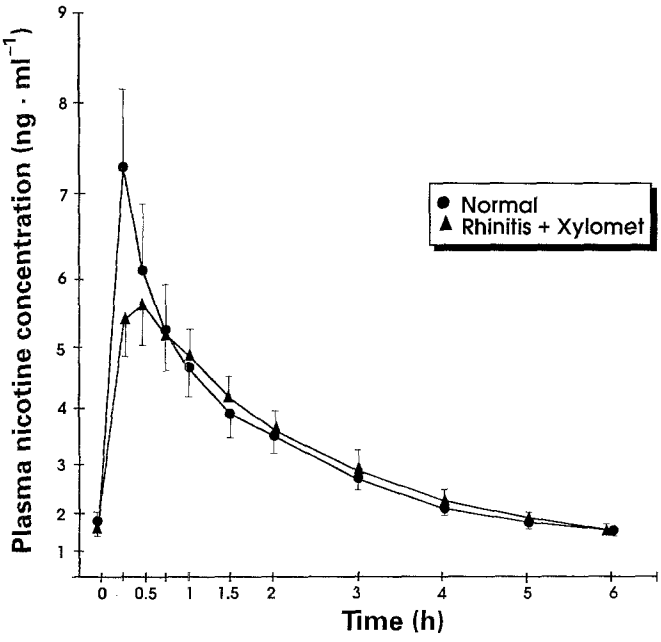

Fig. 1 Mean with SEM plasma nicotine concentrations in fifteen subjects with infectious rhinitis, after concomitant use of a topical decongestant, and in normal health, following an intranasal spray of 2 mg nicotine. For clarity the plasma concentration-time curve for rhinitis without concomitant xylometazoline, which was very similar to that for rhinitis + xylometazoline, has been omitted

Results

Plasma nicotine levels and pharmacokinetic parameters

Mean uncorrected plasma nicotine levels were very similar in the disease-free state and during rhinitis and rhinitis plus xylometazoline. Mean plasma levels are shown in Fig. 1.

The mean (SD) peak plasma concentration (C_{max}) corrected for baseline nicotine concentration in rhinitis was 4.7 (2.3) ng · ml^{-1} compared to 6.0 (3.4) ng · ml^{-1} in the disease-free state. A C_{max} of 4.6 (2.3) ng · ml^{-1} was found during rhinitis plus concomitant use of the decongestant (Table 1).

Time to peak concentration (t_{max}) was inversely related to C_{max}. Accordingly, t_{max} occurred later in rhinitis, at 0.40 (0.16) h than in the disease-free state, at 0.28 (0.09) h. The t_{max} was further prolonged to 0.52 (0.22) h in rhinitis treated with xylometazoline.

The area under the plasma concentration-time curve extrapolated to infinity (AUC_{inf}) corrected for baseline nicotine concentration in rhinitis and in rhinitis with xylometazoline was estimated to be 15.9 (5.81) ng · ml^{-1} · h and 18.9 (6.67) ng · ml^{-1} · h, respectively. The AUC_{inf} during the disease-free state was 17.9 (7.69) ng · ml^{-1} · h (Table 1). The mean elimination half-life estimated in the disease-free state was 3.6 h and in rhinitis with and without the decongestant it was 3.4 h.

Pharmacokinetic interactions

Common cold/rhinitis vs disease-free state

The mean bioavailability of intranasal nicotine was similar in common cold/rhinitis and in the disease-free state. The geometric mean of the ratio $AUC_{rhin.}/AUC_{norm.}$ was 0.93 (90 % CI 0.78–1.12).

The peak plasma concentration ratio was 0.81 (0.67–0.98), and the ratio of the times to peak concentration was 1.36 (1.12–1.64); the latter was significantly longer in common cold/rhinitis compared to the disease-free state ($P < 0.01$). As the 90 % confidence intervals were outside the bioequivalence ranges, 0.8–1.25 for AUC_{inf} and C_{max} and 0.7–1.43 for t_{max}, common cold/rhinitis as compared to the disease-free state was not considered equivalent, neither in terms of the rate nor of the extent of nicotine absorption.

Common cold/rhinitis plus decongestant vs disease-free state

When xylometazoline was given 30 min prior to the nicotine nasal spray during the common cold/rhinitis, the area under the nicotine plasma concentration-time curve was somewhat larger than when the nicotine spray was used during normal health. The geometric mean of the AUC-ratio was 1.11 (90 % CI 0.98–1.33). This was outside the upper limit of the equivalence range for the extent of bioavailability (0.8–1.25), indicating that at least as much nicotine was available to the systemic circulation during common cold/rhinitis after pretreatment with decongestant as in the disease-free state.

There was significantly slower nicotine absorption when the rhinitis was treated with the vasoconstrictor decongestant as compared to the disease-free state, as indicated both by a lower C_{max} ($P < 0.05$) and a later t_{max} ($P < 0.001$). On applying conventional bioequivalence criteria, the two experimental situations could not be considered to be equivalent; the geometric means of the ratios of C_{max} and t_{max} were 0.79 (0.65–0.95) and 1.72 (1.43–2.08), respectively.

Adverse events

Most commonly reported adverse events were sneezing, irritation in the throat and headache. All events were rated as mild by the subjects, except for one report of headache that was rated as moderate. The latter was reported in the common cold/rhinitis session and so could not be discriminated from the symptoms of the disease itself.

Table 1 Pharmacokinetic parameters calculated from plasma nicotine concentration data after 2 × 1 mg nicotine from a nasal spray during rhinitis, with/without the nasal decongestant xylometazoline and in normal health. $n = 15$

	AUC (ng · ml^{-1} · h)[a]			C_{max} (ng · ml^{-1})[a]			t_{max} (h)[b]		
Subject no.	Normal	Rhinitis	Rhinitis + xylometazoline	Normal	Rhinitis	Rhinitis + xylometazoline	Normal	Rhinitis	Rhinitis + xylometazoline
Mean	17.9	15.9	18.9	6.03	4.71	4.58	0.25	0.40	0.50
S.D.	7.69	5.81	6.67	3.36	2.27	2.30	–	–	–
Min.	5.70	9.54	10.36	3.20	2.00	1.60	0.25	0.25	0.25
Max.	36.1	28.9	38.4	13.8	11.1	12.1	0.50	0.75	1.00
Prob.	NS	NS		NS	NS		$P = 0.01$	$P = 0.033$	
	NS			NS			$P < 0.001$		

[a] Corrected for baseline nicotine concentration
[b] Median

Discussion

Nasal administration of nicotine has recently found pratical use as an aid in smoking withdrawal programmes [8, 9]. Disease affecting the nasal mucosa, e.g. inflammation with nasal obstruction and nasal discharge, may interfere with the absorption of intranasally administered nicotine, so it might be necessary to adjust the dose during a cold.

In the present study we applied the methodology of bioequivalence testing rather than testing the null-hypothesis of equality between disease and non-disease states to demonstrate whether the pharmacokinetics of intranasally administered nicotine was affected to a clinically relevant extent by rhinitis and by a topical decongestant. This could not be concluded if the classical hypothesis testing of no difference between the two situations had been tested. Instead, it is necessary to show that the rate and extent of absorption of intranasal nicotine in the disease and non-disease states were equivalent, i.e. the ratios of C_{max} and AUC (and their 90% confidence intervals) were contained within the clinically accepted range of 0.8 to 1.25. That would ensure that the consumer risk would not exceed 5%.

Recent studies have shown that the absorption permeability of the nasal mucosa is decreased during inflammation, e.g. during active seasonal allergic rhinitis at the end of the pollen season [10], as well as during a common cold (corona-virus induced rhinitis) [11]. A possible explanation for the reduced absorption is the exudation of bulk plasma into the subepithelial tissues and into the airway lumen [12].

A further complicating factor for drugs given topically in the nose during a common cold is concomitant treatment with a locally administered vasoconstrictor. In rhinitis it has previously been demonstrated that there is an increase of 22% (from 41 to 50 ml · min^{-1} · 100 g^{-1} tissue) in the nasal mucosal blood flow compared to the disease-free state [13]. When a topical vasoconstrictor is given there is a reduction of 53% (from 50 to 23 ml · min^{-1} · 100 g^{-1} tissue) in the increased blood flow [13]. Thus, the nasal mucosal blood flow in the common cold after treatment with a local vasoconstrictor is approximately 40% lower than in the disease-free state.

In the present study we demonstrated that rhinitis reduced the mean peak plasma nicotine concentration and significantly prolonged the time to peak concentration of intranasally administered nicotine. Pretreatment with xylometazoline further prolonged the absorption time in comparison with untreated rhinitis without affecting the peak plasma nicotine level. As the extent of absorption was largely unaffected, the data indicate slowing of the absorption process. The reduced rate of nicotine absorption during the common cold was probably the result of slower access of nicotine to the subepithelial capillaries in the well vascularised nasal mucosa [12], and the further reduction found after pretreatment with the vasoconstrictor was the result of a decrease in the nasal mucosal blood flow [13].

The bioequivalence ranges adopted in the present study were 0.8–1.25 for the extent of bioavailability and the maximum plasma concentration, and 0.7–1.43 for the time to reach maximum concentration. In general, the appropriate bioequivalence range should be chosen on clinical grounds. Thus, for a drug like nicotine, with a broad therapeutic range and the self-titration behaviour of smokers [14], wider confidence limits should be considered.

The results suggest that a minor proportion of those quitting smoking with the help of a nicotine nasal spray may experience a minor reduction of the effect during common cold/rhinitis. However, the nicotine self-titration behaviour found with most smoking cessation products (except the nicotine patch) will automatically lead to adjustment of the dosage to achieve the desired effect.

Acknowledgements The study was supported in part by grants from the Swedish Medical Research Council (Project no. 8308) and the Medical Faculty at the University Hospital of Lund.

References

1. Pontiroli AE, Calderara A, Pozza G (1989) Intranasal Drug Delivery. Potential advantages and limitations from a clinical pharmacokinetic perspective. Clin Pharmacokinet 17: 299–307
2. Russel MAH, Jarvis MJ, Feyerabend C (1980) A new age for snuff? Lancet I: 474–475
3. Russel MAH, Jarvis MJ, Feyerabend C, Fernö O (1983) Nasal nicotine solution: a potential aid to give up smoking? Br Med J 286: 683–684
4. Jarvis MJ, Hajek P, Russel MAH, West RJ, Feyerabend C (1987) Nasal nicotine solution as an aid to cigarette withdrawal: a pilot clinical trial. Br J Addict 82: 983–988
5. Schneider NG (1992) Nicotine therapy in smoking cessation. Pharmacokinetic considerations. Clin Pharmacokinet 23(3): 169–172
6. Jackson GG, Dowling HF, Spiesman IG, Boand AV (1958) Transmission of the common cold to volunteers under controlled conditions. Arch Intern Med 101: 267–278
7. Olsson P, Kuylenstierna F, Johansson C-J, Gunnar PO, Bende M (1991) Pharmacokinetics of nicotine after intranasal administration. In: Adlkofer F (ed) Effects of nicotine on biological systems. Advances in pharmacologica sciences. Birkhäuser, Basel, pp 57–61
8. Sutherland G, Stapleton JA, Russell MAH et al (1992) Randomised controlled trial of nicotine nasal spray in smoking cessation. Lancet 340: 324–329
9. Hjalmarsson A, Franzon M, Westin Å, Wiklund O (1994) Effect of nicotine nasal spray in smoking cessation. A randomised, placebo-controlled, double-blind study. Arch Int Med 154: 2567–2572
10. Greiff L, Wollmer P, Svensson C, Andersson M, Persson CGA (1993) Effect of seasonal allergic rhinitis on airway mucosal absorption of chromium –51 labelled EDTA. Thorax 48: 648–650
11. Greiff L, Svensson C, Andersson M, Åkerlund A, Wollmer P, Alkner U, Persson CGA (1993) Increased exudative responsiveness in allergen and corona virus-induced airway inflammation. Allergy 48: 91
12. Persson CGA, Erjefält I, Alkner U, Baumgarten C, Greiff L, Gustafsson B, et al (1991) Plasma exudation as a first line respiratory mucosal defence. Clin Exp Allergy 21: 17–24
13. Bende M (1983) The effect of topical decongestant on blood flow in normal and infected nasal mucosa. Acta Otolaryngol (Stockh) 96: 523–527
14. Russell MAH (1976) Tobacco smoking and nicotine dependence. In: Gibbins, et al (eds) Researche advances in alcohol and drug problems, vol 3. Wiley, New York, pp 1–47