Eur J Clin Pharmacol (1998) 54: 521–528

PHARMACODYNAMICS

T. Hummel · C. Rothbauer · E. Pauli · G. Kobal

Effects of the nasal decongestant oxymetazoline on human olfactory and intranasal trigeminal function in acute rhinitis

Received: 7 January 1998 / Accepted in revised form: 6 May 1998

Abstract *Objective*: The placebo-controlled, randomized, double-blind study was performed to investigate dose-related effects of oxymetazoline on olfactory function during the course of the spontaneously occurring cold.
Methods: Drug effects were assessed using olfactory/trigeminal event-related potentials (ERPs) and psychophysical measures (intensity ratings, odor discrimination, butanol threshold); nasal volume was monitored by means of acoustic rhinometry. The investigation was performed in 36 subjects (mean age 24.6 years). The subjects were assigned to treatment groups A, B or C (three groups with 12 subjects each; six women and six men per group). All the subjects received placebo on the left side; on the right side, group A subjects received placebo and group B and C subjects received 0.25 $mg \cdot ml^{-1}$ and 0.5 $mg \cdot ml^{-1}$ oxymetazoline, respectively. After onset of the rhinitis (day 0) measurements were performed on days 2, 4, 6 and 35.
Results: Oxymetazoline clearly produced an increase in nasal volume. However, during the 2-h observation period, effects produced by the two dosages were not significantly different. Despite the increase in nasal volume, oxymetazoline produced only an increase of the overall intensity of H_2S stimuli; it had no systematic effect on other measures of olfactory or trigeminal function. In addition, after all the subjects had recovered from the cold, oxymetazoline had no significant main effect on olfactory/trigeminally mediated sensations.
Conclusions: Oxymetazoline appeared to have neither negative nor major positive effects on intranasal chemosensory function. It is hypothesized that oxymetazoline needs to be applied locally to the area of the olfactory cleft in order to significantly improve olfaction during the course of the common cold.

Key words Nasal congestion · Oxymetazoline

The experiments were carried out in the Department of Experimental and Clinical Pharmacology and Toxicology, University of Erlangen-Nuremberg, Germany

T. Hummel (✉)
Department of Otorhinolaryngology, University of Dresden, Fetscherstrasse 74, D-01307 Dresden, Germany
e-mail: hummeltc@compuserve.com
Tel.: +49-351-458-4420; Fax: +49-351-458-4326

T. Hummel
Smell and Taste Center,
Department of Otorhinolaryngology: Head and Neck Surgery, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania, USA

C. Rothbauer · G. Kobal
Department of Experimental and Clinical Pharmacology and Toxicology, University of Erlangen-Nuremberg, Erlangen, Germany

E. Pauli
Department of Neurology, University of Erlangen-Nuremberg, Erlangen, Germany

Introduction

Oxymetazoline is routinely used in acute rhinitis. As with other α-adrenergic agents, it has been shown to significantly reduce congestion of the nasal cavity when applied intranasally ([1, 2]; for review see [3]). Oxymetazoline is also known for its relatively long duration of action of 6–8 h [4, 5]. Although this drug is used extensively [6], like other over-the-counter medications for the treatment of the common cold, so far no systematic study has investigated its effects on human olfactory function during the course of the cold. In addition, it is not known whether oxymetazoline itself produces olfactory dysfunction as has been noted earlier [7]. Such possible adverse effects may be due, for example, to either direct toxic effects of the administered spray [8] or to the decreased mucosal blood flow itself, which in turn may interfere with inflammatory defense mechanisms leaving the mucosa relatively less well protected [9].

Our experiment addressed two questions: (1) Is there a dose-related effect of oxymetazoline on intranasal chemosensitivity during the course of the common cold? (2) Does oxymetazoline exhibit an influence on olfactory and trigeminal sensitivity in healthy subjects?

Psychophysical testing of olfactory function was performed by means of the "Sniffin' Sticks" pen-like odor dispensing devices [10]. This is an established, standardized test of olfactory function for which normative data exist. In addition to the measurement of odor thresholds, it allows a detailed assessment of the subject's ability to identify and discriminate odors [11, 12]. It is currently used in more than 20 clinics throughout Europe. Chemosensory event-related potentials (CSERPs) in response to intranasal trigeminal and olfactory stimuli were used as an electrophysiological measure of olfactory sensations [10]. This test is typically used for the "objective" evaluation of patients with anosmia or hyposmia [13], or other clinical applications such as the testing of patients with neurological disorders, (e.g. temporal lobe epilepsy [14], Parkinson's disease [15, 16] or multiple sclerosis [17]).

Materials and methods

The study was designed as a placebo-controlled, randomized, double-blind investigation. The Ethics Committee of the University of Erlangen-Nürnberg approved the study, which was performed in accordance with the Declaration of Helsinki on biomedical research (Tokyo amendment). Subjects gave written informed consent when entering the study. A total of 36 volunteers participated [18 women, 18 men; mean age 24.6 years (range 19–36 years), mean weight 69 kg (range 54–90 kg), mean height 176 cm (range 160–193 cm)]. Before onset of the cold all subjects were in excellent health, as established by a thorough physical examination and a detailed history. This examination also ruled out the presence of allergic, vasomotor, chronic, drug-induced and atrophic rhinitis or nasal polyps. The acute onset of the cold was characterized as the presence of a "sneezy", burning or running nose, and at least one of the following symptoms: "feeling feverish", "feeling ill", headache or increased lacrimation. Subjects were advised not to drink alcohol on the evening before measurements, to get sufficient sleep and not to eat or smoke or drink anything other than water 1 hour before measurements. Before each session the investigator obtained a brief history of the subject, overlooking the time since the last encounter. In addition, subjects were given a brief physical examination.

Subjects were randomly assigned to treatment groups A, B or C (three groups with 12 subjects each; 6 women, 6 men). Placebo was always administered to the left nostril. Subjects in group A also received placebo in the right nostril. Subjects in groups B and C received oxymetazoline in dosages of $0.25\ mg \cdot ml^{-1}$ and $0.5\ mg \cdot ml^{-1}$, respectively. The dosages compare to those found in typical over-the-counter preparations, e.g. Larylin, which contains $0.5\ mg \cdot ml^{-1}$ oxymetazoline. Two sprays each of either placebo or oxymetazoline were applied to the left and right nostril 15 min before the session started. Subjects were not allowed to use oxymetazoline or other drugs during the cold. This schedule was performed to assess the acute effects of oxymetazoline on olfactory function.

Each subject participated in four sessions. After onset of the rhinitis (day 0) sessions were performed on days 2, 4, 6 and 35; if one of these days happened to be a Sunday, sessions took place 1 day later. In an additional training session at day 0 or day 1 subjects were thoroughly acquainted with the experimental procedures. They were also trained in a special breathing technique (velopharyngeal closure [18, 19]). All sessions took place at the same time of day (± 2 h; compare [20]). Recording of olfactory and trigeminal event-related potentials (ERPs) in response to intranasal chemical stimuli was followed by psychophysical tests of olfactory function. A break of 15 min separated the two sessions, each of which lasted approximately 60 min.

CSERPs were recorded in response to randomized stimulation of the left and right nostril with two concentrations of the olfactory stimulant H_2S (4 ppm and 8 ppm) and a single concentration of the trigeminal stimulant CO_2 (45% v/v). The stimuli were applied 12 times each to the left and right nostril (stimulus duration 200 ms, interval 40 s; for details of the stimulation technique see [21]). To monitor possible changes in attention which might influence ERP recordings [22], auditory ERPs were obtained in response to 20 stimuli (100 ms stimulation, 95 dB HL, 2 kHz bursts) applied during the 40-s intervals between the chemical stimuli (compare [23]).

Subjects also underwent an odor discrimination task (triple forced choice, 16 pairs of odorants); thresholds were tested for butanol [11]. The volume of the left or right anterior nasal cavity was assessed with acoustic rhinometry (Stimotron-Rhinoklack, Wendelstein, Germany). Three measurements were performed: before drug administration with the subjects being adapted for at least 10 min to room air conditions (baseline), after the CSERP recording approximately 1 h after drug administration and after the psychophysical tests approximately 2 h after drug administration. Measurements were taken over a length of 3 cm starting at the nasal valve [24, 25].

EEG was recorded from 5 positions of the 10/20 system referenced to linked ear lobes (A1 + A2); eye blinks were monitored at Fp2. The system's bandpass was 0.2–30 Hz, the sampling frequency of the stimulus-linked EEG segments of 2048 ms was 250 Hz including a baseline of 530 ms. ERP analysis was performed off-line after averaging (see [21]). Single recordings contaminated by eye blinks (absolute amplitude $> 50\ \mu V$) were discarded in case they appeared from 100 to 800 ms after stimulus onset. Latencies and amplitudes of ERP peaks N1 and P2 were measured and an average across corresponding measures obtained from the 5 recording sites was submitted to further evaluation (see Fig. 3, insert). When collecting ERP data, subjects were requested to perform a tracking task on a video screen. They had to keep a small square, which was controlled by a joystick, inside a larger one which moved around unpredictably [26]. The task helped to stabilize the subjects' vigilance. After this session subjects rated the overall intensity of the chemical stimuli (CO_2, H_2S) on a "paper and pencil" visual analogue scale of 10 cm in length, whereby the left-hand end of the scale was defined as "no sensation" (0 units) and the right-hand end as "maximum strength sensation" (10 units).

Odor discrimination was performed by means of 16 triplets of odorants; the subjects' task was to identify one of three odor pens that had a different smell (for details see [11]). Odor thresholds were assessed for serial dilutions of butanol in water, that were established as geometric rows with a dilution ratio of 1:2 starting with a 4% solution. Using a triple forced-choice paradigm, thresholds were determined by means of a multiple staircase method [27]. Three odor pens were presented in a randomized order, two of which contained solvent and one the odorant in a certain dilution; subjects then had to identify the pen which smelled different. Triplets were presented approximately every 20 s, until the subject had correctly discerned the odorant in two successive trials which triggered a reversal of the staircase. The mean of the last four staircase reversal points (from a total of seven) was used as threshold. Subjects had no immediate feedback regarding the accuracy of their decision.

All data were analysed by means of SPSS 6.1.3 for Windows. Data were submitted to analyses of variance [ANOVA, averaged *F*-test, degrees of freedom corrected according to Greenhouse-Geisser; alpha level 0.05; for each ANOVA both *F* and *P* values and the observed power (pwr) at the 0.05 level is reported]. To answer the question of whether oxymetazoline has a dose-related

Table 1 Measurements obtained for the treated nostril after recovery from the cold. Means (*M*) and standard errors (*SEM*) of event-related potential (ERP) amplitudes and latencies ($10 \leqq n \leqq 12$) for the four different stimuli (4 ppm H_2S, 8 ppm H_2S, 45% v/v CO_2, 2 kHz auditory stimulus). ERP components to chemical stimuli were obtained after stimulation of the treated (right) nostril. In addition, the table shows overall intensity ratings of H_2S and CO_2 (in estimation units), data for the results of the right-sided testing of odor discrimination (number of items correct from 16 items) and odor thresholds (thresholds in dilution steps). It also presents volumetric data (in ccm) obtained for the right nasal cavity 1 h and 2 h after drug administration. All data were obtained at day 35 after onset of the cold

		Placebo		0.25 mg·ml^{-1}		0.5 mg·ml^{-1}	
		M	SEM	M	SEM	M	SEM
Amplitude	H_2S 4 ppm	−3.9	0.5	−3.9	0.9	−4.4	0.5
N1	H_2S 8 ppm	−5.1	0.7	−4.7	0.8	−4.7	0.7
(μV)	CO_2	−6.2	1.1	−5.6	2.2	−5.3	0.8
	Auditory	−7.4	0.7	−8.1	0.9	−7.6	0.8
Amplitude	H_2S 4 ppm	7.6	1.0	7.3	1.2	6.6	0.7
P2	H_2S 8 ppm	6.4	0.9	8.8	1.4	7.4	1.1
(μV)	CO_2	9.1	1.1	13.5	2.7	9.3	1.1
	Auditory	12.0	1.8	13.1	1.6	11.8	1.1
Latency	H_2S 4 ppm	419	15	425	26	413	16
N1	H_2S 8 ppm	397	13	404	23	388	12
(ms)	CO_2	388	16	423	18	393	15
	Auditory	131	7	143	8	132	6
Latency	H_2S 4 ppm	604	17	614	35	592	13
P2	H_2S 8 ppm	567	20	591	24	567	15
(ms)	CO_2	554	20	597	13	596	17
	Auditory	271	14	285	21	257	17
Overall H_2S intensity		5.5	0.6	5.9	0.7	7.2	0.9
Overall CO_2 intensity		8.4	0.7	8.1	0.7	9.3	0.4
Odor discrimination		11.7	0.7	11.6	0.5	11.0	0.7
Odor thresholds		7.5	0.9	6.3	0.9	7.4	0.7
Nasal volume (after 1 h)		3.3	0.3	4.9	0.4	4.9	0.4
Nasal volume (after 2 h)		3.7	0.5	5.4	0.4	5.6	0.4

effect on intranasal sensitivity, only measures obtained for the treated (right) nostril were analysed (between-subject factor "drug" and within-subject factor "session"; additional factor "H_2S concentration" introduced for analysis of olfactory ERPs). Results obtained for the untreated (left) nostril can be found in [28]. To answer the question of whether oxymetazoline affects olfactory function in healthy subjects, dose-related effects of oxymetazoline were investigated at day 35 (between-subject factor "drug", within-subject factor "nostril"; additional factor "H_2S concentration" introduced for analysis of olfactory ERPs).

Results

Descriptive statistics of investigated parameters are presented in Table 1 for the right nostril at day 35 after recovery from the cold (ERP data, results from psychophysical tests and acoustic rhinometry). One subject was not included in the data analysis because of suspected alcohol abuse, which became known after all the exper-

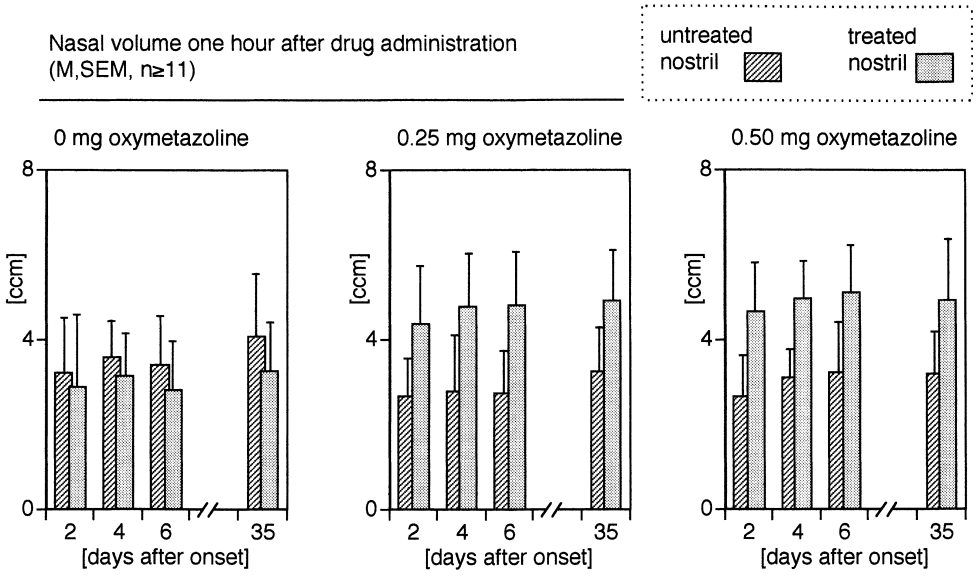

Fig. 1 Means and standard errors of means ($11 \leqq n \leqq 12$) of volumetric measurements of the leftsided (untreated) and the right-sided (treated) nasal cavity 1 h after drug administration (placebo, 0.25 mg·ml^{-1} and 0.50 mg·ml^{-1} oxymetazoline), obtained at days 2, 4, 6 and 35 after onset of the cold. Oxymetazoline produced an increase of the nasal patency; the effects produced by the two dosages of oxymetazoline were not significantly different from each other

iments had been performed. Due to technical problems with the data storage system, acoustic rhinometry datasets of 11 subjects were only partially available for analysis. In addition, due to excessive blinking, only a subset of ERP data for four subjects could be analysed.

Right nasal volume before treatment increased throughout the period of testing [(factor "session": $F(3,93) = 3.00$, $P = 0.045$, pwr = 0.69; factor "drug": $F(2,31) = 0.65$, $P = 0.53$, pwr = 0.15) (Fig. 1)]. An effect of the factor "drug" became significant both 1 h and 2 h after administration of oxymetazoline [after 1 h: factor "drug": $F(2,27) = 14.09$, $P < 0.001$, pwr = 1.0; after 2 h: $F(2,27) = 7.87$, $P = 0.002$, pwr = 0.93]. However, no significant differences were observed ($t < 0.63$, $P > 0.53$) when investigating differential effects of the two dosages of oxymetazoline by means of *t*-tests separately for the four sessions and the two points of measurement after drug administration. Overall, oxymetazoline had a strong effect on nasal congestion; consequently, a significant effect of the factor "session" was not found [after 1 h: $F(3,81) = 0.67$, $P = 0.54$, pwr = 0.19; after 2 h: $F(3,81) = 0.18$, $P = 1.65$, pwr = 0.42].

Oxymetazoline produced an increase of H_2S overall intensity ratings [factor "drug": $F(2,31) = 4.62$, $P = 0.018$, pwr = 0.74 (Fig. 2a)], i.e. odor stimuli were rated as most intense when the highest dose of oxymetazoline was used, while they were perceived as weakest by the group who received placebo. No significant changes were found throughout the course of the cold [factor "session": $F(3,93) = 2.17$, $P = 0.11$, pwr = 0.54]. No such changes were found for CO_2 intensity ratings [factor "drug": $F(2,31) = 0.77$, $P = 0.47$, pwr = 0.17], although these ratings increased as the subjects recovered from the cold [factor "session": $F(3,93) = 13.28$, $P < 0.001$, pwr = 1.0]. In addition, oxymetazoline had no effect on olfactory thresholds or odor discrimination [factor "drug": odor thresholds $F(2,32) = 2.40$, $P = 0.107$, pwr = 0.45; odor discrimination $F(2,32) = 1.26$, $P = 0.299$, pwr = 0.25) (Fig. 2b)]. However, olfactory function was found to improve throughout the course of the cold [factor "session": odor thresholds $F(3,96) = 3.31$, $P = 0.032$, pwr = 0.74; odor discrimination $F(3,96) = 2.39$, $P = 0.085$, pwr = 0.58].

Oxymetazoline also had no major effect on olfactory ERPs [factor "drug": $F(2,27) < 1.90$, $P > 0.17$, $0.09 <$ pwr < 0.36 (Fig. 3)]. Only P2 amplitudes showed a significant effect of the factor "session" [$F(3,81) = 2.93$, $P = 0.041$, pwr = 0.68] and an interaction between factors "session" and "drug" [$F(6,81) = 4.24$, $P = 0.001$, pwr = 0.97]. This interaction indicated that P2 amplitudes increased as subjects recovered from the cold. The interaction "session" by "drug" was difficult to interpret because the findings were inconsistent for the two concentrations of H_2S. For all other olfactory ERP measures, the factor "session" and the interaction "session" by "drug" did not reach the level of significance ["session": $F(3,81) < 2.44$,

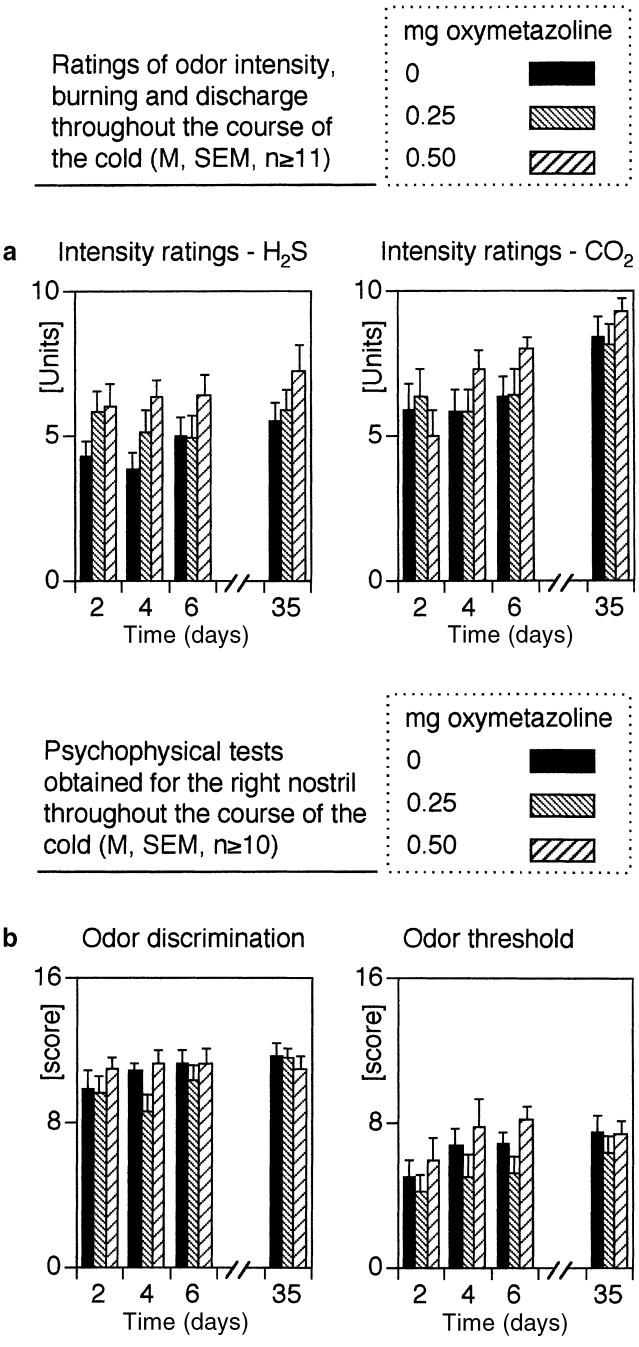

Fig. 2a, b Means and standard errors of means ($11 \leqq n \leqq 12$) of overall intensity ratings of H_2S and CO_2 stimuli. Results are shown for placebo and the two dosages of oxymetazoline (0.25 mg·ml^{-1} and 0.50 mg·ml^{-1}), obtained at days 2, 4, 6 and 35 after onset of the cold. Ratings were made on a visual analogue scale (0 = no sensation, 10 = maximum strength sensation). A significant effect of the factor "drug" was found for H_2S intensity ratings. **b** Means and standard errors of means ($11 = n = 12$) of butanol odor thresholds and results from the odor discrimination task after right-sided testing. Results are shown for placebo and the two dosages of oxymetazoline (0.25 mg·ml^{-1} and 0.50 mg·ml^{-1}), obtained at days 2, 4, 6 and 35 after onset of the cold. Thresholds are expressed in dilution steps – the higher the dilution step, the higher the subjects' sensitivity. Results of the odor discrimination task are expressed as the number of items that were correctly identified (from a total of 16 items)

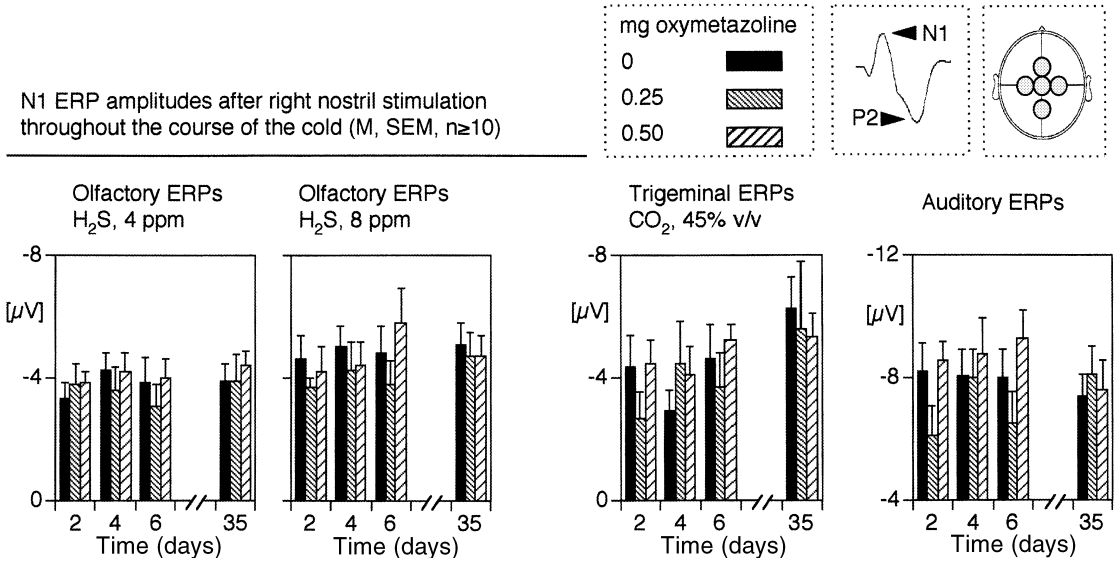

Fig. 3 Means and standard errors of means ($10 \leqq n \leqq 12$) of N1 amplitudes of trigeminal and olfactory event-related potentials (*ERP*s) after stimulation of the treated nostril; results for auditory ERPs are also shown. Results are presented for placebo and the two dosages of oxymetazoline (0.25 mg·ml^{-1} and 0.50 mg·ml^{-1}), obtained at days 2, 4, 6 and 35 after onset of the cold. The insert on the top right shows schematic drawings of an ERP and the five recording positions; ERP peaks N1 and P2 are identified by arrows

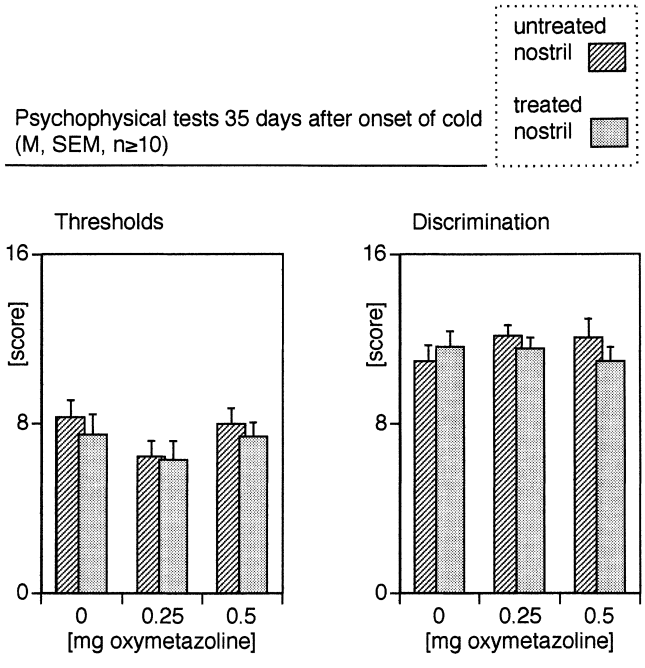

Fig. 4 Means and standard errors of means ($10 \leqq n \leqq 12$) of butanol odor thresholds and results from the odor discrimination task after testing of the treated and untreated nostril. Results are shown for placebo and the two dosages of oxymetazoline (0.25 and 0.50 mg·ml^{-1}), obtained at day 35 after onset of the cold. Thresholds are expressed in dilution steps – the higher the dilution step the higher the subjects' sensitivity. Results of the odor discrimination task are expressed as the number of items that were correctly identified (from a total of 16 items). Oxymetazoline had no significant effect on psychophysical measures of olfactory function

$P > 0.07$, $0.21 <$ pwr < 0.59; "session" by "drug": $F(6,81) < 1.70$, $P > 0.13$, $0.28 <$ pwr < 0.61]. The factor "H_2S concentration" became significant for N1 and P2 amplitudes [$F(1,27) = 5.91$, $P = 0.022$, pwr $= 0.65$; $F(1,27) = 18.7$, $P < 0.001$, pwr $= 0.99$] and N1 and P2 peak latencies [$F(1,27) = 9.57$, $P = 0.005$, pwr $= 0.85$; $F(1,27) = 24.5$, $P < 0.001$, pwr $= 1.0$]. This indicated that olfactory ERP amplitudes increased, while latencies shortened as a function of stimulus concentration (compare Fig. 3, Table 1).

Trigeminal ERPs were not influenced by oxymetazoline [factor "drug": $F(2,28) < 1.27$, $P > 0.29$, $0.09 <$ pwr < 0.25] or the factor "session" [$F(3,84)$] $= 2.89$, $P = 0.064$, $0.07 <$ pwr < 0.67], no interactions between factors "drug" and "session" were observed [$F(6,84) < 1.24$, $P > 0.30$, $0.13 <$ pwr < 0.46]. No drug effects were found for auditory ERPs which had been recorded as controls [factor "drug": $F(2,29) < 3.16$, $P > 0.058$, $0.06 <$ pwr < 0.56; "drug" by "session": $F(6,87) < 1.70$, $P > 0.15$, $0.35 <$ pwr < 0.61]. However, for the P2 amplitude an effect of the factor "session" became significant [$F(3,87) = 3.90$, $P = 0.015$, pwr $= 0.81$], indicating that the late amplitude of auditory ERPs decreased with repetitive measurements.

When comparing drug effects on day 35, oxymetazoline was found to produce an increase in nasal volume (Fig. 1), although these changes were not related to the dosage of oxymetazoline [baseline: factor "drug" $F(2,32) = 1.49$, $P = 0.24$, pwr $= 0.29$; factor "nostril" $F(1,32) = 1.59$, $P = 0.22$, pwr $= 0.23$; "drug" by "nostril": $F(2,32) = 1.22$, $P = 0.31$, pwr $= 0.25$; after 1 h: factor "drug" $F(2,32) = 0.57$, $P = 0.57$, pwr $= 0.14$; factor "nostril" $F(1,32) = 15.3$, $P < 0.001$, pwr $= 0.97$; "drug" by "nostril": $F(2,32) = 14.5$, $P < 0.001$, pwr $= 1.0$; after 2 h: factor "drug" $F(2,32) = 3.20$, $P = 0.06$, pwr $= 0.57$; factor "nostril" $F(1,32) = 18.6$, $P < 0.001$, pwr $= 0.99$; "drug" by "nostril": $F(2,32) = 3.99$, $P = 0.030$,

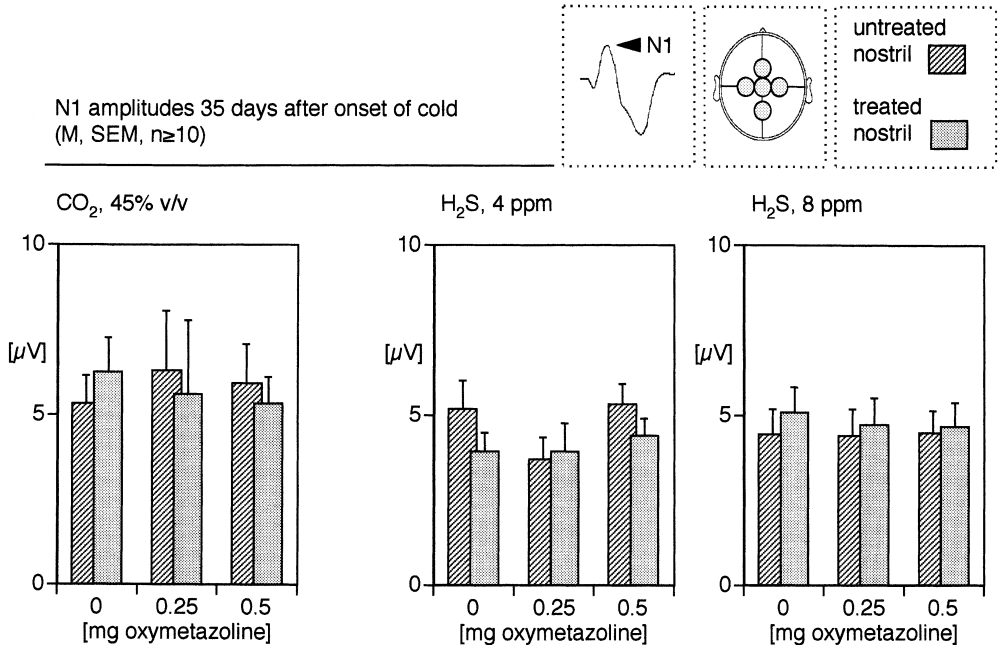

Fig. 5 Means and standard errors of means ($10 \leqq n \leqq 12$) of N1 amplitudes of trigeminal and olfactory ERPs after stimulation of the treated and untreated nostril. Results are shown for placebo and the two dosages of oxymetazoline (0.25 and 0.50 $mg \cdot ml^{-1}$), obtained at day 35 after onset of the cold. The insert on the top right shows schematic drawings of an ERP and the five recording positions; ERP peaks N1 and P2 are identified by arrows. The decongestant had no significant effect on N1 amplitudes

pwr = 0.67 (Table 1)]. However, no effect of oxymetazoline was found for overall ratings of H_2S intensity [factor "drug": $F(2,34) = 1.30$, $P = 0.29$], overall ratings of CO_2 intensity [factor "drug": $F(2,34) = 1.02$, $P = 0.37$ (Fig. 2a)], odor thresholds [factor "drug": $F(2,32) = 1.51$, $P = 0.24$, pwr = 0.30, "drug" by "nostril": $F(2,32) = 0.14$, $P = 0.87$, pwr = 0.07], or odor discrimination [factor "drug": $F(2,32) = 0.19$, $P = 0.83$, pwr = 0.08, "drug" by "nostril": $F(2,32) = 1.79$, $P = 0.18$, pwr = 0.35 (Fig. 2b, Fig. 4)]. In addition, oxymetazoline had no significant influence on trigeminal ERPs [factor "drug": $F(2,30) < 2.99$, $P > 0.06$, $0.05 <$ pwr < 0.54; interaction "drug" by "nostril": $F(2,30) < 2.60$, $P > 0.09$, $0.16 <$ pwr < 0.48] or olfactory ERPs [factor "drug": $F(2,31) < 0.63$, $P > 0.54$, $0.05 <$ pwr < 0.34; interaction "drug" by "nostril": $F(2,31) < 0.56$, $P > 0.57$, $0.05 <$ pwr < 0.30] (Fig. 5). Only the significant interaction "drug" by "H_2S concentration" [$F(2,31) = 5.83$, $P = 0.007$, pwr = 0.84] for the P2 amplitude indicated that the late olfactory ERP amplitude increased when oxymetazoline was used; this was not the case when placebo was applied (Fig. 6).

Discussion

The study provided three major findings: (1) Oxymetazoline produced an increase in nasal volume; however, there was no significant difference between effects produced by the two dosages. (2) Despite this increase in nasal volume, oxymetazoline only produced an increase of overall intensity ratings of H_2S stimuli; it had no systematic effect on other measures of olfactory or trigeminal function. (3) After all subjects had recovered from the cold, oxymetazoline exhibited no significant major effect on olfactory/trigeminally mediated sensations.

As expected, oxymetazoline produced a highly significant increase in the volume of the anterior nasal cavity. However, contrary to previous findings ([2, 29]; for review see [3, 30]), it was observed that the two dosages produced almost identical effects. One reason why the two dosages of oxymetazoline did not produce different effects may be the short observation period. In fact, as indicated by the mean nasal volume 2 hours after administration (Table 1), the higher dosage appeared to produce a slightly greater effect. This may have become even more pronounced, had the observation period been longer. Another explanation may simply be found in a ceiling effect, which may be present at a dosage of 0.25 $mg \cdot ml^{-1}$. The latter explanation would argue for a reduction of the dosage used in standard oxymetazoline over-the-counter preparations (e.g. Larylin).

Despite the strong effect on the volume of the anterior nasal cavity, it was surprising to see that the only dose-related effect of oxymetazoline on olfactory function was on H_2S intensity ratings; none of the other measures of chemosensory function were affected. It appears possible that the improved patency of the nasal cavity may have contributed to the increase of the ratings; specifically, as subjects were offered only one scale to rate odor intensity, the increased patency may have indirectly enhanced odor intensity ratings within the

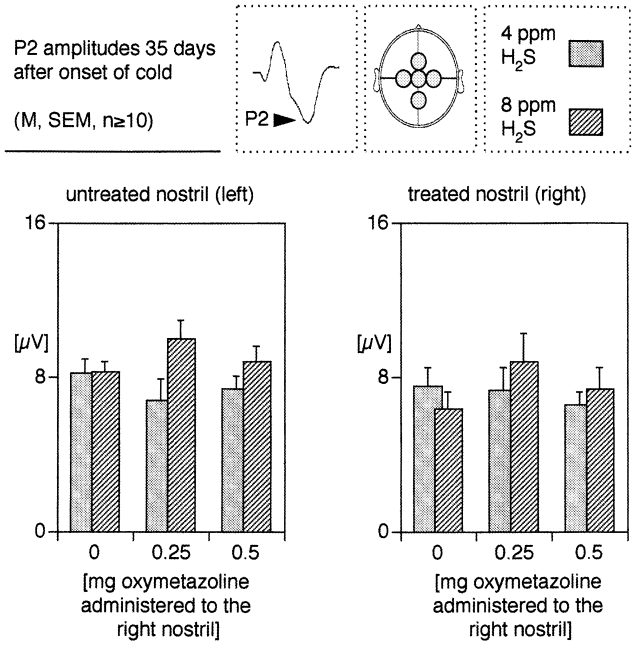

Fig. 6 Means and standard errors of means ($10 \leq n \leq 12$) of P2 amplitudes of olfactory ERPs after stimulation of the treated and untreated nostril. Results are shown for placebo and the two dosages of oxymetazoline (0.25 and 0.50 $mg \cdot ml^{-1}$), obtained at day 35 after onset of the cold. The insert on the top right shows schematic drawings of an ERP and the five recording positions; the ERP peak P2 is identified by arrows. The significant interaction "drug" by "H_2S concentration" indicated that the P2 amplitude increased when oxymetazoline was used; this was not the case when placebo had been applied

context of the "halo-dumping" effect [31]. In addition, it has been shown that external nasal dilators affect odor intensity ratings [32]; this was interpreted in terms of a "perceptual constancy model", where "a decrease in nasal resistance decreases perceived sniff vigour and so produces an increase in perceived odor intensity". This may also apply to the use of nasal decongestants, which increased perceived odor intensity but had only a small effect on other, less biased measures of olfactory function.

The relatively minor effect of oxymetazoline on olfaction may also be due to the small portion of the spray that presumably reached the area above the middle turbinate. In fact, research performed by means of gamma camera scans [33, 34] or endoscopic photography [35] indicates that the largest portion of a nasal spray is deposited in the anterior nasal cavity. Future experiments will focus on olfactory changes when oxymetazoline is directly applied to the middle and superior turbinate.

Investigations in subjects who had recovered from the cold did not indicate that oxymetazoline had a negative effect on olfactory and trigeminal function. That is, oxymetazoline exerted no dose-related changes on chemosensations, although it clearly increased nasal volume. As this portion of the study was performed in healthy subjects with little mucosal discharge, in this case it must be emphasized that oxymetazoline probably had access to large portions of the olfactory epithelium. Therefore, identification of possible toxic effects of oxymetazoline would have been much more likely than in measurements performed during the course of the cold.

In conclusion, oxymetazoline appeared to have neither negative nor major positive effects on intranasal chemosensory function. It is hypothesized that nasal decongestants need to be applied locally to the area of the olfactory cleft, in order to significantly improve olfaction during the course of the common cold.

Acknowledgements This research was supported by Bayer Vital GmbH & Co. KG, Cologne, Germany and grant P01 DC 00161 from the National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, MD USA. We also would like to thank Dr. Regina Heckenberger, Bayer GmbH, for excellent technical assistance and we are indebted to Drs. Sybille Barz and Konrad Grosser for help during the collection of the data. In addition, we greatly appreciate the comments of Dr. Tyler Lorig, Washington and Lee University, Lexington, VA, USA.

References

1. Bende M (1983) The effect of topical decongestant on blood flow in normal and infected nasal mucosa. Acta Otolaryngol (Stockh) 96: 285–288
2. Akerlund A, Klint T, Olen L, Rundcrantz H (1989) Nasal decongestant effect of oxymetazoline in the common cold: an objective dose-response study in 106 patients. J Laryngol Otol 103: 743–746
3. Smith MB, Feldman W (1993) Over-the-counter cold medications: a critical review of clinical trials between 1950 and 1991. JAMA 269: 2258–2263
4. Horsal BM, Horsal SA, Hurwitz JJ, Freeman JL (1995) A rationale for the selection of nasal decongestants in lacrimal drainage surgery. Ophthal Plast Reconstr Surg 11: 215–220
5. Bailey BJ (1969) Clinical evaluation of a topical nasal decongestant – oxymetazoline. Eye Ear Nose Throat Monthly 48: 46–59
6. Taylor JG (1992) The common cold. In: Krogh CM, Carruthers-Czyzewski, Travill L (eds) Self-medication: reference for health professionals, 4th ed. Canadian Pharmaceutical Association, Ottawa, Ontario, pp 191–212
7. Henkin RI (1994) Drug-induced taste and smell disorders. Drug Saf 11: 318–377
8. Berg OH, Henriksen RN, Steinsvag SK (1995) The effect of a benzalkonium chloride-containing nasal spray on human respiratory mucosa in vitro as a function of concentration and time of action. Pharmacol Toxicol 76: 245–249
9. Bende M, Fukami M, Arfors KE, Mark J, Stierna P, Intaglietta M (1996) Effects of oxymetazoline drops on acute sinusitis in the rabbit. Ann Otol Rhinol Laryngol 105: 222–225
10. Kobal G, Hummel T, Sekinger B, Barz S, Roscher S, Wolf SR (1996) "Sniffin' Sticks": Screening of olfactory performance. Rhinology 34: 222–226
11. Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G (1997) "Sniffin' Sticks": olfactory performance assessed by the combined testing of odor identification, odor discrimination, and olfactory thresholds. Chem Senses 22: 39–52
12. Klimek L, Hummel T, Moll B, Kobal G, Mann WJ (1998) Lateralized and bilateral olfactory function in patients with chronic sinusitis compared to healthy controls. Laryngoscope 108: 111–114
13. Kobal G, Hummel T (1998) Olfactory and intranasal trigeminal event-related potentials in anosmic patients. Laryngoscope 108: 1033–1035

14. Hummel T, Pauli E, Stefan H, Kettenmann B, Schüler P, Kobal G (1995) Chemosensory event-related potentials in patients with temporal lobe epilepsy. Epilepsia 36: 79–85
15. Hawkes CH, Shephard BC, Daniel SE (1997) Olfactory dysfunction in Parkinson's disease. J Neurol Neurosurg Psychiatry 62: 436–446
16. Barz S, Hummel T, Pauli E, Majer M, Lang CJG, Kobal G (1997) Chemosensory event-related potentials in response to trigeminal and olfactory stimulation in idiopathic Parkinson's Disease. Neurology 49: 1424–1431
17. Hawkes CH, Shephard BC, Kobal G (1997) Assessment of olfaction in multiple sclerosis: evidence of dysfunction by olfactory evoked response and identification tests. Brain 62: 436–446
18. Nagel WA (1904) Einige Bemerkungen über nasales Schmecken. Z Psychol 25: 268
19. Kobal G, Hummel T (1989) Brain responses to chemical stimulation of the trigeminal nerve in man. In: Green BG, Mason JR, Kare MR (eds) Chemical Senses, Vol. 2: Irritation. Dekker, New York, pp 123–139
20. Lötsch J, Nordin S, Hummel T, Murphy C, Kobal G (1997) Chronobiology of nasal chemosensitivity: do odor or trigeminal pain thresholds follow a circadian rhythm? Chem Senses 22: 593–598
21. Kobal G, Hummel T (1994) Olfactory (chemosensory) event-related potentials. Toxicol Ind Health 10: 587–596
22. Näätänen R, Paavilainen P, Tiitinen H, Jiang D, Allho K (1993) Attention and mismatch negativity. Psychophysiology 30: 436–450
23. Hummel T, Cramer O, Mohammadian P, Geisslinger G, Pauli E, Kobal G (1997) Comparison of the antinociception produced by two oral formulations of ibuprofen: ibuprofen effervescent vs. ibuprofen tablets. Eur J Clin Pharmacol 52: 107–114
24. Min YG, Jang YJ (1995) Measurements of cross-sectional area of the nasal cavity by acoustic rhinometry and CT scanning. Laryngoscope 105: 757–759
25. Roithmann R, Cole P, Chapnik J, Barreto SM, Szalai JP, Zamel N (1994) Acoustic rhinometry, rhinomanometry, and the sensation of nasal patency: a correlative study. J Otolaryngol 23: 454–458
26. Kobal G, Hummel C, Nürnberg B, Brune K (1990) Effects of pentazocine and acetylsalicylic acid on pain-rating, pain-related evoked potentials and vigilance in relationship to pharmacokinetic parameters. Agents Actions 29 3/4: 342–359
27. Doty RL (1991) Olfactory system. In: Getchell TV, Doty RL, Bartoshuk LM, Snow JBJ (eds) Smell and taste in health and disease. Raven Press, New York, pp 175–203
28. Hummel T, Rothbauer C, Barz S, Grosser K, Pauli E, Kobal G (1998) Olfactory function in acute rhinitis. Ann N Y Acad Sci (in press)
29. Akerlund A, Arfors KE, Bende M, Intaglietta M (1993) Effect of oxymetazoline on nasal and sinus mucosal blood flow in the rabbit as measured with laser-Doppler flowmetry. Ann Otol Rhinol Laryngol 102: 123–126
30. Johnson DA, Hricik JG (1993) The pharmacology of alpha-adrenergic decongestants. Pharmacotherapy 13: 110S–115 S
31. Clark CC, Lawless HT (1994) Limiting response alternatives in time-intensity scaling: an examination of the halo-dumping effect. Chem Senses 19: 583–594
32. Hornung DE, Chin C, Kurtz DB, Kent PF (1997) Nasal dilators affect intensity ratings of olfactory stimuli. Chemical Senses 22: 704
33. Hardy JG, Lee SW, Wilson CG (1985) Intranasal drug delivery by spray and drops. J Pharm Pharmacol 37: 294–297
34. Newman SP, Moren F, Clarke SW (1987) Deposition pattern from a nasal pump spray. Rhinology 25: 77–82
35. McGarry GW, Swan IR (1992) Endoscopic photographic comparison of drug delivery by ear-drops and by aerosol spray. Clin Otolaryngol 17: 359–360