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Nasal decongestion with imidazoline derivatives: acoustic rhinometry measurements

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Abstract *Objective*: The objective of this single-blind study was to establish whether there are any differences between conventional imidazoline-containing nasal drops with regard to duration of action and decongestion potential.
Methods: Six different substances were each administered to 108 healthy volunteers (nine groups of 12 adults), respectively, in the concentration recommended for adults (and two also in that recommended for infants) over a period of 8 h in comparison with 0.9% NaCl. The volumetric measurement of the nasal lumen was conducted by means of acoustic rhinometry (Rhinoklack).
Results: The decongestive effect of all imidazoline preparations set in relatively uniformly, without any appreciable differences. After 20 min all the products exhibited approximately 60% of their maximum decongestive effect, which was achieved after approximately 40 min, having produced an increase in volume of approximately 20%. In contrast, in terms of duration of action, considerable differences between the individual products were to be discerned: indanazoline 0.118%, naphazoline 0.02% and tetryzoline 0.1% had no effect whatsoever after 4 h. Oxymetazoline 0.05% and 0.01%, xylometazoline 0.025% and 0.1%, and tramazoline 0.1264% still had an appreciable effect after 4 h, while after 8 h only oxymetazoline 0.05% and 0.01% still had a relevant decongestive effect. A rebound effect associated with reactive hyperaemia was observed after 8 h in all short-acting products (indanazoline, naphazoline, tetryzoline and tramazoline), which in the case of indanazoline was even associated with a reduction in the nasal lumen. Interestingly, there were no differences between the xylometazoline and oxymetazoline concentrations recommended for adults and those for infants in terms of efficacy. The low-dose concentrations of the preparations for infants appear to be sufficient to produce a satisfactory therapeutic effect.

Key words Nasal volume · Nasal decongestion · Imidozoline-derivates

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Introduction

Nasal decongestants for local application develop their pharmacological effect via the activation of postjunctional α-adrenergic receptors at both pre- as well as postcapillary blood vessels of the nasal mucosae, and vasoconstriction is triggered as a result of direct specific binding to the receptor. Substances with this sympathomimetic property include on the one hand the catecholamines (*inter alia* epinephrine or phenylephrine) and on the other the imidazoline derivatives (*inter alia* indanazoline, naphazoline, tetryzoline, tramazoline, oxymetazoline, or xylometazoline). Both types produce an effective action on nasal capacity vessels with α_1 and α_2 adrenoceptors, through which the degree of swelling of the mucous membranes is regulated [1]. Imidazoline also exerts an influence on the resistance vessels (α_2 adrenoceptors), which regulate the blood flow [2]. Catecholamines preferentially address α_1 adrenoceptors, and imidazolines predominantly α_2 adrenoceptors. Thus, swelling of the mucous membranes is diminished and nasal airway patency increased.

Following a relatively rapid onset of action, however, the substances differ in terms of the duration of their action. In contrast to the long-acting imidazolines (6–8 h), a reduction of the effect can already be seen in catecholamines after 1 h [3]. Varying concentrations of the preparations suggest a different quality and duration of effect. Only two scientifically acceptable studies concerning the efficacy of local decongestants of the imidazoline type compared with placebo have been

conducted in the past 30 years [4]. Studies in which the efficacy of different imidazolines have been tested against each other have not been found in the literature.

Acoustic rhinometry is a technique which has now been available for a number of years and which makes it possible to describe the geometry of the nasal cavity in a simple and non-invasive manner. The objective of this study was to investigate the imidazoline-containing nasal drops currently available on the market with regard to their decongestive potential and duration of action in vivo with the aid of reflection acoustics.

Materials and methods

Acoustic rhinometry

For the rhinometric measurements we used a Rhinoklack device supplied by Stimotron (Regensburg, Germany). A sonic tube 100 cm in length and 2 cm in diameter connects the sound source with the nasal cavity via a nose adapter and is fitted with a microphone to record the reflections during a time window of 10 ms. The acrylate-material adapter has a defined length of 75 mm, with a concave opening for fitting against the nasal cavity, and is screwed into place on the sonic tube.

The sound source is controlled by an IBM AT 386-compatible computer that is fitted with an A-D converter. At a click of the mouse the sound impulse is emitted via a spark discharger at a pressure of 55 dB for 0.2 ms and sent into the nasal cavity. The reflections are transformed into an area-distance function of the nasal cavity and epipharynx and depicted graphically.

Due to the superimposition of the epipharyngeal lumen by the lumen of the contralateral nasal passage, the measurements were restricted to the nasal cavity before the choanae. The border between the hard and the soft palate was determined by uttering a guttural sound (K). In the adult subjects, this distance – measured from the nostril – was in all cases considerably greater than 75 mm, which is why the volume measurements were restricted to a distance from the end of the nasal adapter to 75 mm into the nasal cavity.

Subjects

The measurements were recorded at a constant room temperature of 21–23 °C and at constant relative humidity after the subjects had acclimatized themselves for a period of at least 20 min. No strenuous physical activity by the test subjects prior to the measurements was permitted. A total of 108 (nine groups of 12) healthy volunteers aged between 18 and 36 years, participated in the study in the form of case series (60 men and 48 women). Subjects taking any form of medication whatsoever were excluded, particularly any patients with relatively long-term use of local decongestants. In the event that nasal drops had been taken over the short term, a washout period of at least 2 days had to be adhered to before the start of the investigation. Thirty-eight percent of the test subjects were smokers (28 men, 13 women). Subjects with acute or chronic rhinitis, sinusitis, or other inflammations in the nasotracheal region, including otitis media, were excluded from participation, as were subjects with previous history of surgery of the nose or of the paranasal sinuses and subjects with anatomic changes such as septum deviation or polyps. Furthermore, care was taken to ensure that none of the test subjects presented with any disorders associated with impairment of mucociliary function (Kartagener's syndrome, Sjögren's syndrome, cystic fibrosis, or immotile cilia syndrome).

Active substances

In this single-blind study, investigations were conducted only with α-sympathomimetic imidazolines (xylometazoline 0.025% and 0.1%, oxymetazoline 0.01% and 0.05%, indanazoline 0.118%, naphazoline 0.02%, tetryzoline 0.1% and tramazoline 0.1%) as monopreparations (i.e. without any other chemicals as persatives) in conventional concentrations versus physiological saline solution as placebo (Table 1).

Firstly, in order to determine the best measuring time, a pilot study involving six test subjects was run over 24 h, in which the decongestive effect of 0.3-ml doses of xylometazoline 0.1% was measured before administration, 15 and 30 min after administration, and subsequently every 30 min. This pilot study confirmed that almost the maximum degree of decongestion was achieved after approximately 30 min. The highest decongestion values were obtained on average after 210 min. After 540 min the nasal volume had returned to its original volume, which after 24 h was somewhat smaller than the volume initially measured. The final measurement schedule was defined on the basis of these preliminary results.

Study design

All substances were investigated in the single-blind design in case series of 12 patients (9 groups). The measurements were made with the test subjects sitting freely and upright in the end-expiration phase in order to avoid measurement errors [5]. Investigation time 0 was baseline without administration of nasal drops. This was followed by administration of 0.3 ml of each of the respective solutions using a disposable insulin syringe (Omnifix Duo 40 IU, Braun, Melsungen, Germany) into the two nostrils, and distribution of the solution in the nasal cavity by sniffing. The subjects were not permitted to blow their noses. Measurements were repeated 20 min (investigation time 1) and 40 min (time 2) after the administration. The findings of the pilot series using xylometazoline 0.1% led to the expectation that roughly the maximum degree of decongestion is achieved within this period of time [6]. The last two measurements were made 240 and 480 min (investigation times 3 and 4, respectively) after the baseline measurement.

Table 1 Average volume increase (X) at different investigation times for all tested substances (NS = nominal $P > 0.05$)

Substance	Difference 0–1 (ccm)			Difference 0–2 (ccm)				Difference 0–3 (ccm)			Difference 0–4 (ccm)		
	X	SE	Nominal P	X	SE	Corrected p	Nominal P	X	SE	Nominal P	X	SE	Nominal P
Xylometazoline 0.025%	5.9	1.3	<0.001	5.3	1.3	<0.01	<0.005	5.1	1.7	<0.05	0.8	1.8	NS
Xylometazoline 0.1%	4.9	1.6	<0.05	5.7	1.5	<0.05	<0.005	6.9	1.7	<0.005	1.8	1.8	NS
Oxymetazoline 0.05%	3.9	1.1	<0.005	5.4	0.9	<0.001	<0.0001	4.4	0.8	<0.0001	3.0	1.2	<0.05
Oxymetazoline 0.01%	6.8	1.5	<0.01	6.2	1.4	<0.005	<0.001	6.8	1.8	<0.005	4.6	1.7	<0.05
Tetryzoline 0.1%	6.6	3.6	<0.005	7.2	4.0	<0.05	<0.05	−0.1	3.7	NS	−1.2	3.3	NS
Tramazoline 0.1264%	8.3	2.0	<0.005	7.8	1.7	<0.01	<0.001	5.3	1.8	<0.05	−2.2	2.0	NS
Naphazoline 0.02%	7.8	1.3	<0.0001	6.2	1.3	<0.01	<0.001	3.9	1.9	NS	−1.2	1.3	NS
Indanazoline 0.118%	4.1	0.6	<0.0001	4.4	0.8	<0.005	<0.0001	0.7	0.9	NS	−2.6	1.0	<0.05
NaCl 0.9%	−0.2	1.7	NS	0.9	1.9	NS	NS	2.2	1.5	NS	2.9	2.2	NS

The measurement values were recorded separately for each side by emitting three consecutive sonic waves each of 0.2 ms duration into the nasal cavity. The data were represented graphically immediately afterwards on the monitor as an area-distance function according to the Ware-Aki algorithm [7]. For the two sides of the nose, three separate curves were converted into the nasal volume and the mean value determined arithmetically. The relevant distance covered *per definitionem* the sector from the end of the nasal adapter (75-mm mark) 75 mm into the nasal cavity (150-mm mark). The addition of the two sides yields the total volume of the nasal cavity. A separate assessment of the two sides was dispensed with, since the nasal resistance – and thus the sum of the volumes of the two nasal cavities – remains constant during the nasal cycle [8].

The maximum efficacy of the preparations within the measurement series was anticipated to be at investigation time 2 (40 min after administration). The efficacy hypothesis was thus set in relation to this time point. The efficacy of the respective preparations in contrast to the baseline situation was tested using the two-sided Student's *t*-test for dependent samples (the Shapiro-Wilk test did not reveal deviations from normality). Corrections for multiple testing were done according to Bonferroni-Holm. Homogeneous groups for investigation time 2 were formed exploratively using the LSD method according to Tukey.

Results

In the pilot study with measurements at half-hourly intervals (Fig. 1), an appreciable effect of approximately 60% of the decongestive maximum of xylometazoline 0.1% was already detectable after 15 min. The maximum decongestive effect was observed after 3 h, with an increase in volume of 6.1 cm^3 (19%). After 210 min, there was an almost linear drop in the volume reaching baseline status after 540 min. After 24 h, the nasal volume (measured against the baseline situation) was reduced by 9% – obviously a rebound effect.

In accordance with these preliminary results, the investigation times for all imidazoline derivatives were selected on the assumption of an approximately identical mechanism and duration. Fig. 2 shows the nasal volumes of all test subjects (except 0.9% NaCl), with the maximum decongestive effect after 40 min (investigation time 2), slightly greater than the increase in volume after 20 min. After 8 h (investigation time 4) approximately the original condition was reattained. The maximum decongestion to a value of 37.2 cm^3 compared with the baseline value of 31.2 cm^3 corresponds to an increase in volume of 19.3%.

The varying decongestion potential of the nine individual substances tested here is shown in Fig. 3. Table 1 documents the differences in nasal volumes between the individual investigation times 1–4 and the baseline measurement time 0 for all nine substances. The anticipated lack of any effect of 0.9% NaCl is evident. The lowest increases in nasal volumes after 20 min are shown by oxymetazoline 0.05% at 3.9 cm^3 and indanazoline 0.118% at 4.1 cm^3. The greatest decongestive effect of all the preparations under investigation was shown by tramazoline 0.1264% after 20 min with 8.3 cm^3 (26.7%). The decongestive effect of all other preparations took the form of an increase in volume of between 4 cm^3 and 8 cm^3. This effect was relevant for all preparations, except 0.9% NaCl as placebo. Differences between the individual substances could not be clearly distinguished. However, xylometazoline in the 0.025% concentration – recommended for use in infants – had a similar decongestive efficacy (5.9 cm^3) at time 1 as the 0.1% concentration recommended for adults (4.9 cm^3). This was also the case for the 0.01% concentration of oxymetazoline recommended for infants (6.8 cm^3) compared with the 0.05% concentration for adults (3.9 cm^3).

At investigation time 2 after 40 min, there was a significant enlargement of the nasal lumen for all

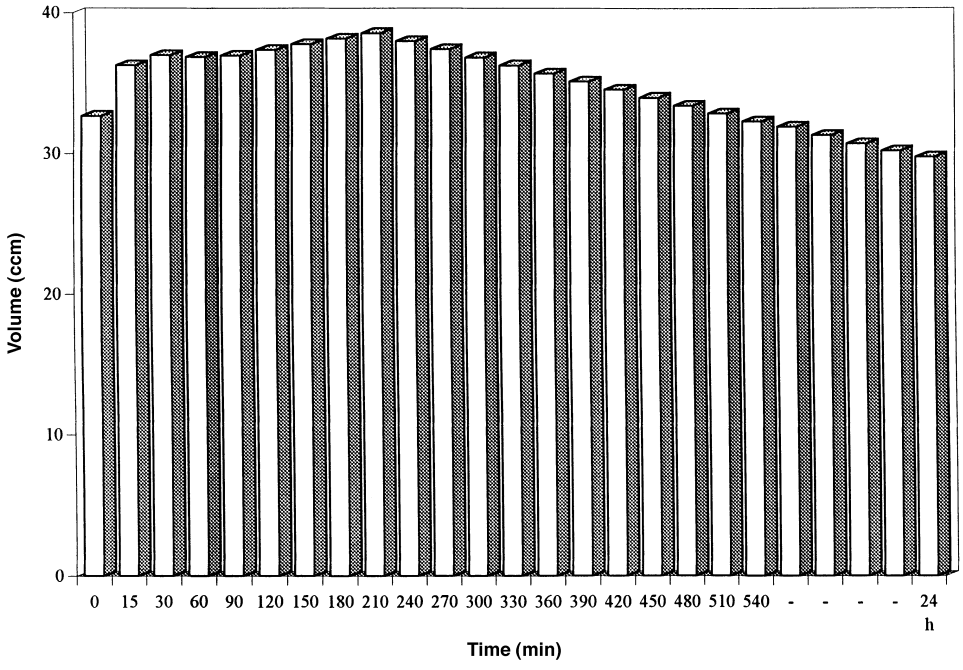

Fig. 1 Pilot study over 24 h (xylometazoline 0.1%; $n = 6$) with half-hourly intervals demonstrating a rapid onset of action with an increase of nasal volume 15 min after application and maximum after 3.5 h

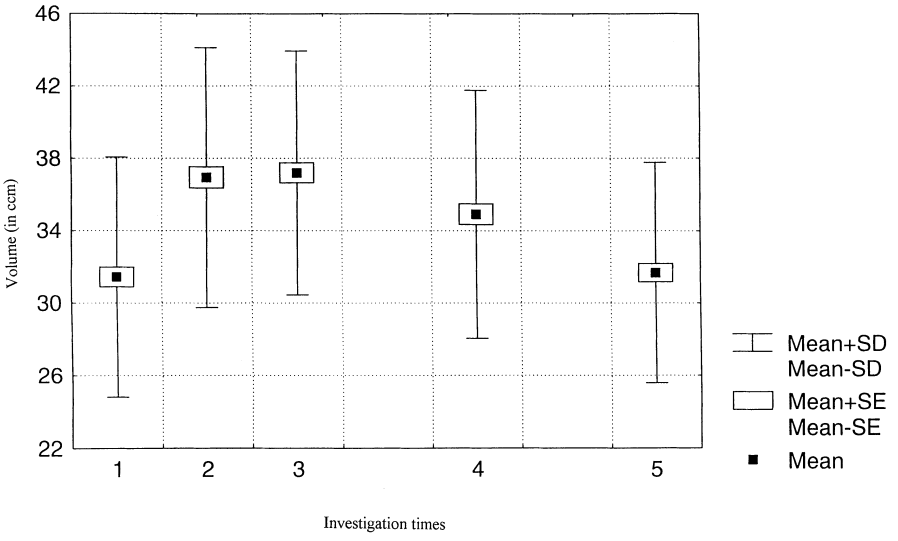

Fig. 2 Box plot volumes of all imidazolines except placebo ($n = 96$) against investigation times

preparations except placebo (Table 1; all corresponding P values of < 0.05 for investigation time 2 after correction for multiple testing). Compared among each other, the following groups display no differences in mean value (homogeneity test according to Tukey): on the one hand placebo and indanazoline; on the other all imidazoline derivatives. Compared with investigation time 1, xylometazoline 0.1% oxymetazoline 0.05%, tetryzoline 0.1% and indanazoline 0.118% produced a further increase in volume, whereas xylometazoline 0.025%, oxymetazoline 0.01%, tramazoline 0.1264% and naphazoline 0.02% showed a slight loss of efficacy compared with investigation time 1 after 20 min.

At investigation time 3 after 240 min, xylometazoline 0.1% and oxymetazoline 0.01% were the only preparations seen to produce any further increase in volume. In all other preparations, the efficacy dropped after 240 min. In the case of tetryzoline 0.1%, indanazoline 0.118%, and naphazoline 0.02% a therapeutical effect could no longer be discerned after this time point. Relevant therapeutic effects evident after 240 min were given only by xylometazoline 0.025% and 0.1%, oxymetazoline 0.05% and 0.01% and tramazoline 0.1264% (nominal $P < 0.05$), but even tramazoline 0.1264%, which initially produced a very good effect, showed a pronounced reduction in efficacy.

At investigation time 4 after 480 min, all substances showed a loss of efficacy. At this stage relevant effects were shown only by oxymetazoline 0.05% and 0.01% (nominal $P < 0.05$). Just as was the case for tramazoline 0.1264%, the short-acting preparations tetryzoline 0.1%, indanazoline 0.118% and naphazoline 0.02%

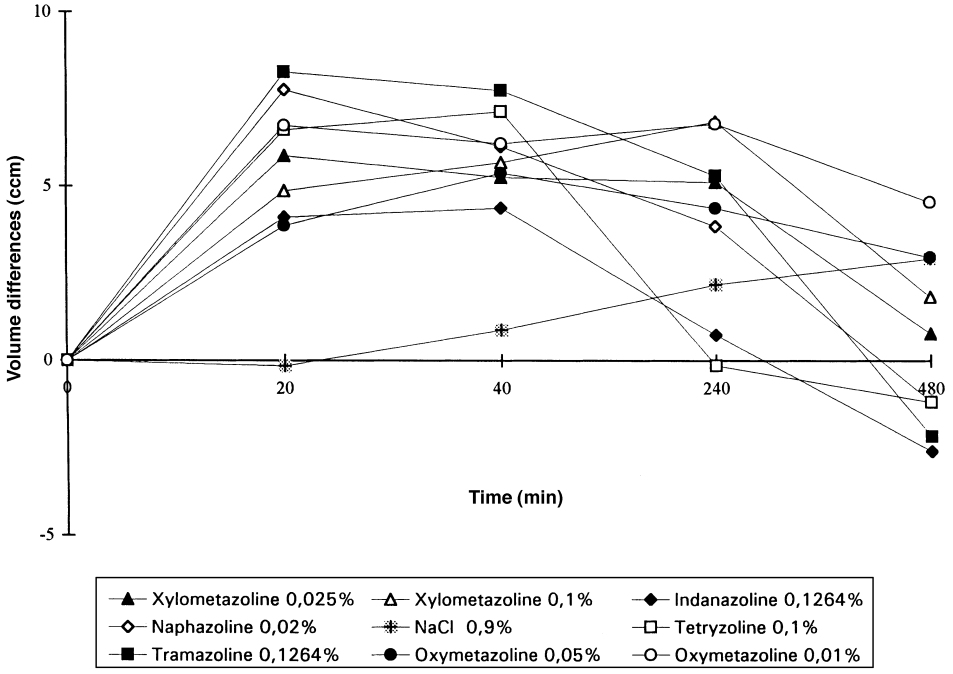

Fig. 3 Time-dependent increase of nasal volumes for the different imidazoline-derivates. Time points are not proportional

were now all associated with a reduction in the nasal lumen compared with the baseline measurement; this reduction was relevant for indanazoline 0.118% ($P < 0.05$).

Discussion

Numerous investigations have been conducted since the introduction of the reflection-acoustic measurement technique by Jackson in 1977 [9] and the modified nasal approach by Hilberg in 1989 [10] to test the reliability of the method of measurement [7, 11–17]. The accuracy of measurement is excellent back to the region of the choanae, which in adults is roughly 7.5 cm distant from the nostril opening. Beyond the choanae, however, the method proves to be fraught with problems, due to the superimposition of the other side of the nose and the expanse of the tracheal cavity [13]. In our investigations of the effects of decongestant nasal drops on the nasal lumen, we therefore restricted ourselves to this proximal region.

Various conventional imidazoline preparations all produced a maximum decongestion already after 20–40 min, after which time the effect evenly dropped off. The more rapid onset of action compared with the pilot study with xylometazoline is due above all to the fact that indanazoline 0.118%, naphazoline 0.02% and tetryzoline 0.1% have a considerably shorter duration of effect than xylometazoline. Tramazoline 0.1264% is roughly comparable with xylometazoline, while the two oxymetazoline preparations have a pronounced prolonged effect compared with xylometazoline. All imidazoline derivatives had a statistically significant effect compared with 0.9% NaCl. Slight differences between the individual substances as regards their decongestive potential are, however, not statistically significant and must be considered as being within the normal range of variation.

The greatest degree of decongestion measured in the investigations corresponds to an increase in volume of 19.3%. Other authors have found volume increases ranging up to 35% [16, 12] and 42% [18]. Grymer et al. [16] found an increase in nasal volume of 35% in subjects with free nasal respiration; here, however, the nasal cavities were initially flooded with a 0.12% ephedrine solution and then treated with two pump actions of a 0.5% xylometazoline solution. In the investigations conducted by Hilberg et al. [18], half of the test subjects were selected according to the criterion of a pollen allergy. The stronger decongestive effect of nasal drops in these patients can be explained by the increased blood flow in the mucosae [18–20]. It may well be that a higher dose would have produced an even greater degree of enlargement of the nasal cavity. However, on the other hand, xylometazoline 0.025% and oxymetazoline 0.01% (in both cases concentrations actually recommended for infants) appear to have the same effect as the higher concentration solution recommended for adults, meaning that the 0.3 ml dose used here appears to be fully adequate.

While there were thus no evident variations in terms of the quality of effect, to our great surprise the preparations did differ considerably interms of duration of effect. After 8 h, only the two oxymetazoline preparations (both in the concentration recommended for adults as well as in that for infants) had a relevant effect (nominal $P < 0.05$). Indanazoline 0.118% in particular, but also naphazoline 0.02%, tetryzoline 0.1% and tramazoline 0.1264% were seen to result in a swelling of the nasal lumen after 8 h, which was obviously a rebound effect as a result of reactive hyperaemia [21–25]. A similar rebound effect can in all probability also be expected for xylometazoline and oxymetazoline – the half-hourly measurements taken in connection with the administration of xylometazoline in the pilot study over 24 h seem to indicate this; this was however, due to the persistent effect of the substance beyond the measuring range.

The dosages recommended by the manufacturers appear to contradict the decongestive effect measured in this study. For example, it is recommended that naphazoline 0.02% or indanazoline 0.118%, preparations with an extremely short duration of action, should be administered upto a maximum of three to four times daily – an inappropriate dosage recommendation for therapeutic applications. These short-acting substances thus appear to be rather better suited for short-term diagnostic interventions than for the desired, long-term therapeutic decongestion. In view of a duration of effect of approximately 4 h, the single (in some cases repeated) adminstration recommended for xylometazoline appears to be inadequate. Only in the case of oxymetazoline, with a duration of action of 8 h, does the recommended application of two to three times daily appear appropriate.

Irrespective of the duration of action, one conspicuous point is that xylometazoline 0.025% as well as oxymetazoline 0.01% (in both cases concentrations recommended for infants) both produce the same effect in adults as the concentrations of the respective substances actually recommended for adults, i.e. xylometazoline 0.1% and oxymetazoline 0.05%. This gives rise to the question as to whether the concentration of the solutions has not been selected at a too high level, for use in both adults and in infants, insofar as infants actually require such medication at all. The effect of the imidazolines appears to follow an ''all-or-nothing'' principle from a certain minimum concentration upwards; animal experiments appear to confirm the identically favourable effect of preparations containing a very low dose of the respective substance [24]. In addition, the relatively high concentration might also be responsible for a stronger rebound effect [24]. The conclusions drawn here may also be considered applicable for inflammatory hyperaemic nasal mucosae, particularly considering the fact that hyperaemic nasal mucosae are seen to be subject to a better decongestive

effect. Comparable measurements in connection with inflammation and allergy are, however, still lacking at present.

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