Rhinology, 33, 14-17, 1995

Sustained use of xylometazoline nasal spray shortens the decongestive response and induces rebound swelling*

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SUMMARY

Long-term use of topical vasoconstrictors for the nose may result in rhinitis medicamentosa, drug addiction and tachyphylaxis. Some authors also believe that the severity of rebound swelling is proportional to the period during which the drug has been used, the frequency of its administration, and the amount of drug given. It has previously been reported that four-week use of the recommended dose of oxymetazoline induces rebound swelling, a sign of rhinitis medicamentosa. To study the effect of an increased amount of vasoconstrictor on rebound swelling and the decongestive effect of the drug, nine healthy subjects were given xylometazoline nasal spray in double the recommended dose (1.0 mg/ml; 0.28 ml in each nostril thrice daily) for 30 days. After 30 days on xylometazoline, the decongestive effect was the same 1 h after drug administration as before starting the medication. Similarly, after 30 days on xylometazoline, the decongestive effect was less 5 h after drug administration than it was 6 h after drug administration at the start of medication ($p < 0.005$). After 10 days no rebound swelling was recorded, but after 30 days rebound swelling occurred in eight out of nine subjects ($p < 0.05$). When comparing the results of this trial with the corresponding results of the oxymetazoline study, no further increase in rebound swelling was found. We conclude that long-term use of xylometazoline nasal spray shortens the decongestive response in healthy volunteers. Moreover, double the recommended dose of xylometazoline did not further increase the rebound swelling seen when using the recommended dose of oxymetazoline.

Key words: xylometazoline, rhinitis medicamentosa, rebound swelling, topical vasoconstrictors

INTRODUCTION

Prolonged use of topical vasoconstrictors in the nose may lead to rhinitis medicamentosa and drug addiction. When the vasoconstrictive effect of the drug has disappeared, nasal stuffiness occurs because of rebound swelling. It has been suggested that drug addiction develops after sustained use of these drugs since the patient has to use more frequent and larger daily doses to relieve the stuffiness. This phenomenon is called tachyphylaxis (Baldwin, 1977; Black et al., 1980; Toohill et al., 1981). Various authors have shown that the same dose of the vasoconstrictor has the same decongestive effect after long-term use (Petruson, 1981; Åkerlund et al., 1991; Graf et al., 1994a). This finding agrees with the clinical impression that patients derive much benefit from the decongestants even after prolonged use (Fleece et al., 1984). However, the reason for increasing the number of daily doses may be that the duration of the decongestive effect of the drug is reduced by sustained use; this possibility has been proposed earlier, but never objectively investigated (Jarvis, 1969). It has also been suggested, but never demonstrated, that the severity of rebound swelling is proportional to the length of time the drug has been used, the frequency of its administration, and the amount of drug given (Kully, 1945; Chigwell, 1972; Baldwin, 1977; Fleece et al., 1984). Our study was performed on healthy subjects who instilled oxymetazoline nasal spray (0.5 mg/ml; 0.1 ml thrice daily) for 30 days. The recordings were performed with rhinostereometry, which is a very accurate optical method for measuring nasal mucosal swelling. At the end of the month, rebound swelling and increased histamine sensitivity were present and were interpreted as signs of rhinitis medicamentosa and nasal hyperreactivity, respectively. We concluded that the rebound swelling was caused by vasodilatation rather than oedema (Graf et al., 1994a; Graf et al., 1994b). The aim of the present study was to investigate whether the duration of the decongestive effect decreases

* Received for publication September 15, 1993; accepted May 22, 1994

after sustained use of a topical vasoconstrictor. An additional aim was to determine whether the long-term use of vasoconstrictor in double the recommended dose further increased the rebound swelling recorded following the recommended dose (Graf et al., 1994a).

MATERIAL AND METHODS

Nine volunteers (eight women and one man; 18-41 years old) were included in the study which was performed from September 1991 to April 1992. They were all healthy and had no history of allergy or other diseases of the nose. Before entering the trial, they were examined and found to have normal rhinoscopic findings. Xylometazoline (Otrivin®) nasal spray was supplied by Ciba-Geigy in original 10-ml bottles (1.0 mg/ml). The nasal mucosa swelling was recorded by rhinostereometry, which is an optical, non-invasive direct method for making measurements. The apparatus consists of a microscope placed on a micrometer table that can be moved in three angular directions establishing a three-dimensional coordinate system. The test subject is fixed exactly to the apparatus using a tooth splint adapted to the teeth. The nasal cavity can be visualized through the ocular lens and, since the microscope has a small depth of focus, changes in the position of the medial mucosal surface of the concha inferior can be recorded along a milimeter scale. The accuracy of the method is 0.2 mm (Juto et al., 1982). Both at the start of the study and before the treatment with the nasal spray the baseline position of the nasal mucosa was determined. This was done by making repeated recordings of the concha inferior in both nasal cavities at noon, after an acclimatization period of 30 min. One to five days later, the mucosal baseline positions were recorded at noon, as before. Thereafter, the volunteer sprayed 0.28 ml (2 puffs) of xylometazoline (1.0 mg/ml) into each nostril, after 1 h and 6 h the mucosal positions were determined. The subjects were then asked to spray 0.28 ml of xylometazoline (1.0 mg/ml) thrice daily into each nostril at fixed hours. After 10 and 30 days on the drug, the subject did not use the spray in the morning. On these days, at 14-17 h after the last dose of xylometazoline, the mucosal baseline positions were recorded at noon. After 29 days, the xylometazoline nasal spray was applied. After 1 h and 5 h, the mucosal positions were again determined. After 29 days the subjects stopped using the spray and new recordings of the mucosal baseline positions were performed after 2, 7, and 14 days. After 30 days the volunteers were asked the following questions concerning the last month: (1) Did you have a cold?; and (2) Did you have you a stuffy, runny or dry nose, or nasal bleedings? Two days after they stopped using the spray, they were asked the same questions.

In each subject, the mean value of the mucosal baseline position on each side of the nose before starting the nasal spray served as the reference position. The mean values of changes in the mucosal swelling on each examination were then compared to the reference position. The paired t-tests and analysis of variance (ANOVA) were employed for the statistical analysis. In comparing the results of this trial with those of the study on oxymetazoline (Graf et al., 1994a), the unpaired t-test was used.

RESULTS

Nine subjects completed the study regarding variation in the baseline position. The mean mucosal baseline position for the group was the same after 10 days on xylometazoline as before starting the medication. After 30 days on this therapy, the mean baseline position had increased in eight subjects and ranged from 0.3-2.5 mm. In the group, the mean value increased by 0.9 mm ($p < 0.05$), but 2, 7, and 14 days after terminating the therapy it had returned to its initial value (Figure 1). These results agree with those of the oxymetazoline study (Graf et al., 1994a).

Seven subjects performed the part of the study regarding the decongestive effect of the drug. Two of them failed to do so because they misunderstood the instructions. The remaining seven subjects had almost the same decongestive effect at 1 h after drug administration, both before starting and 29 days after medication. The mean decongestive effect was 1.5 mm at both recordings (Figure 2). However, after another 5 h the mean

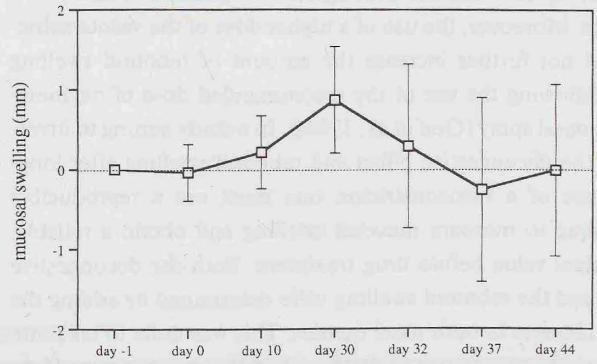

Figure 1. Changes in the mean nasal mucosa swelling of both concha inferior in nine healthy subjects before, during 30-day use of xylometazoline (1.0 mg/ml; 0.28 ml in each nostril, thrice daily), and after stopping the medication. The swelling on day -1 served as the reference position. The recordings on days 10 and 30 were made 14-17 h after administration of the spray. The error bars denote the 95% confidence intervals. Rebound swelling was present after 30 days ($p < 0.05$).

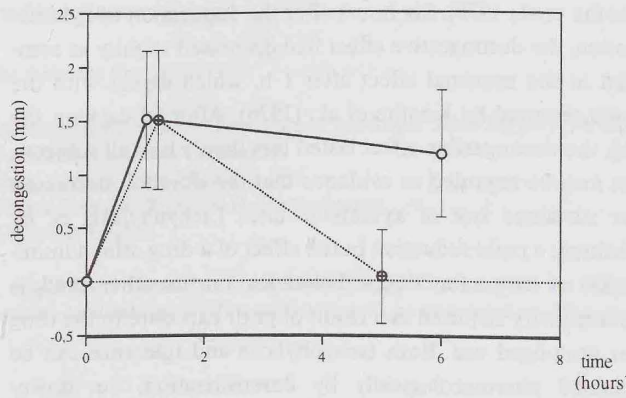

Figure 2. The mean decongestion in both inferior concha in seven healthy subjects who used xylometazoline (1.0 mg/ml; 0.28 ml in each nostril, thrice daily) for 30 days. The zero level represents the reference position of the mucosa before starting the medication. The open circles indicate the mean decongestion at 1 and 6 h after administration of the spray before starting the medication. The filled circles indicate the corresponding decongestion at 1 and 5 h after 30 days on the medication. The error bars denote the 95% confidence intervals. After 30 days, the duration of the decongestive effect had decreased ($p < 0.005$).

decongestive effect still existed, but was decreased from 1.5 to 1.2 mm before starting the medication ($p < 0.05$; Figure 2). After 30 days on the drug, the decongestive effect had disappeared after only 5 h ($p < 0.005$; Figure 2). In all seven subjects the decongestive effect decreased at 5 h following drug administration after 30 days on xylometazoline (mean: 0.04 mm) as compared to the decongestion at 6 h after drug administration at the start of medication (mean: 1.2 mm; $p < 0.005$; Figure 2). After 30 days on the drug all subjects reported nasal stuffiness. Eight subjects also reported stuffiness 1–2 days after the last dose of xylometazoline in the mornings and in the evenings (one subject did not answer this question). Four complained of a runny nose, three of a dry nose, one of nasal bleeding, and two subjects had a common cold during the period. The subjects who had a common cold completed the part of the study regarding the decongestive effect of the drug.

DISCUSSION

This investigation shows that long-term use of xylometazoline nasal spray shortens the decongestive response in healthy volunteers. Moreover, the use of a higher dose of the vasoconstrictor did not further increase the amount of rebound swelling seen following the use of the recommended dose of oxymetazoline nasal spray (Graf et al., 1994a). In a study aiming to investigate the decongestive effect and rebound swelling after long-term use of a vasoconstrictor, one must use a reproducible technique to measure mucosal swelling and obtain a reliable, individual value before drug treatment. Both the decongestive effect and the rebound swelling were determined by adding the mean changes in both nasal cavities. This was done to take into account the occurrence of reciprocal swelling in the nose (Juto et al., 1984). With this technique, no significant day-to-day variation in the baseline position was found before the drug treatment began. The decongestive effect was recorded at 1 h and 6 h after the first instillation of the nasal spray. These intervals were chosen because it has been reported that xylometazoline has its maximal effect after 1 h and this may last up to 9 h (Knothe et al., 1976). Six hours after the application of xylometazoline, the decongestive effect had decreased slightly as compared to the maximal effect after 1 h, which agrees with the results reported by Knothe et al., (1976). After 30 days on the drug, the decongestive effect lasted less than 5 h in all subjects. This may be regarded as evidence that the duration decreased after sustained use of xylometazoline. Tachyphylaxis is, by definition, a rapid reduction in the effect of a drug after administration of only a few doses. Tolerance, on the other hand, is hyporeactivity acquired as a result of prior exposure to the drug after prolonged use. Both tachyphylaxis and tolerance can be explained pharmacologically by desensitization, i.e. down-regulation of the receptors (Ross et al., 1985). No tolerance or true tachyphylaxis occurred in this trial, since the decongestive effect remained unchanged 1 h after administration even after prolonged use, which is in accordance with previous reports (Petruson, 1981; Åkerlund et al., 1991; Graf et al., 1994a). However, our findings in this study may be due to either down-regulation of the α-receptors or an altered affinity to the α-receptors after prolonged use of the drug (Ross et al., 1985). According to the theory of down-regulation, the reason why no change in the decongestive effect was noted at 1 h after the subjects used this medication for 30 days, would be that the amount of vasoconstrictor was large enough to occupy all receptors. Although there was a reduction in the number of receptors, they were numerous enough to induce the same decongestive effect. A down-regulation of receptors may also explain the decreased duration of the effect of the drug. Once a decongestive effect occurs, the vasoconstrictor is released from the receptor. Since the number of receptors is reduced, the duration of the decongestive effect is also reduced. If the theory of altered affinity to a receptor is applied to our findings, the decongestive effect remaines unchanged for 1 h following administration over a prolonged period, because the number of receptors is the same. The altered affinity means that the complex between the receptor and the vasoconstrictor dissolves earlier than when the subject started to use the medication, and this shortens the decongestive response.

When the "nose-drop addict" seeks medical advice he only obtains relief of nasal symptoms by instilling the spray 4–15 times per day according to Baldwin (1977). Thus, the clinical findings are in accordance with the shortened decongestive response seen in this study. The reduction in drug effect must be interpreted to be an expression of tachyphylaxis in a broader sense of the term. To increase the amount of xylometazoline at each administration, we doubled the volume recommended by the manufacturers. The doses of xylometazoline and oxymetazoline recommended for adults by the manufacturers are 0.14 ml (1.0 mg/ml) and 0.1 ml (0.5 mg/ml), respectively, in each nostril thrice a day. An increased volume of nasal spray does not necessarily mean that an increased amount of active drug has been applied to the mucosa. However, it has been reported that 0.2 ml of 0.25 mg/ml oxymetazoline has a stronger decongestive effect than 0.1 ml of the drug in the same concentration (Åkerlund et al., 1989). Moreover, in that study 0.1 ml of 0.5 mg/ml oxymetazoline had the same decongestive effect as 0.2 ml of a 0.25 mg/ml solution. Thus, when using a volume of 0.28 ml, the amount of vasoconstrictor applied must be considered as increased, as compared to that in the recommended dose. It has been reported that 0.5 mg/ml oxymetazoline has the same decongestive effect as 1.0 mg/ml xylometazoline when 0.2 ml of each drug is used (Knothe et al., 1976). Thus, when double the recommended dose of xylometazoline was used in this study, it corresponded to almost three times the amount of vasoconstrictor administered when using the recommended dose of oxymetazoline. Despite the increase in the amount of vasoconstrictor applied to the mucosa in this study, rebound swelling was not further increased as compared to that recorded after using oxymetazoline in the recommended dose (Graf et al., 1994a). Thus, the results of this study do not support the theory that an increased amount of vasoconstrictor has an effect on rebound swelling and on rhinitis medicamentosa (Kully, 1945; Chigwell, 1972; Baldwin, 1977; Fleece et al., 1984).

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