

Effect of a Topical Glucocorticoid, Budesonide, on Nasal Mucosal Blood Flow as Measured with ^{133}Xe Wash-Out Technique

MATS BENDE, NILS LINDQVIST and ULF PIKORIN

Dept. of Oto-Rhino-Laryngology, University Hospital, Lund, Medical Department, AB Draco, Lund, and Dept. of Oto-Rhino-Laryngology, Sahlgren's Hospital, Gothenburg, Sweden

The "vasoconstrictor" effect of dermally applied steroids is a widely used parameter when determining the potency of glucocorticoids. A similar effect on the nasal mucosa has been suggested as providing an explanation for the clinical effect of topically administered glucocorticoids in the treatment of nasal disorders such as allergic and vasomotor rhinitis. The recently described ^{133}Xe wash-out method was used for the purpose of blood flow determination in 11 healthy subjects. In a randomized double-blind cross-over study, the effect of topically administered budesonide, a non-halogenated glucocorticoid, for 1 week was compared with that of placebo. No difference was found to occur in the mucosal blood flow after the administration of budesonide, as compared with placebo. It seems likely that a more complex activity than vasoconstriction is responsible for the clinical effect in the treatment of nasal disorders, and further research is required in order to clarify this issue.

Key words: blood flow; glucocorticoid effect; nasal mucosa; rhinitis.

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Topically administered glucocorticoids have become an established therapy in nasal disorders such as allergic and vasomotor rhinitis (8).

The requirements which the topically administered glucocorticoids are expected to satisfy (high anti-inflammatory properties, and little or no systemic side effects) have been fulfilled by a number of glucocorticoids such as beclomethasone dipropionate and flunisolide. A recently introduced non-halogenated glucocorticoid, budesonide, has been shown to possess similar properties (4, 14). This glucocorticoid has been shown to be clinically effective in the treatment of seasonal as well as perennial allergic rhinitis (1, 11, 12).

Although the clinical effect of topically administered glucocorticoids is undisputed, the mode of action of the beneficial effect in allergic and vasomotor rhinitis is still imperfectly understood (13). When glucocorticoids are ap-

plied on the skin, a "vasoconstriction", visible as a blanching phenomenon, is seen after some hours. This phenomenon, which occurs in all subjects, has been widely used in the grading of glucocorticoid potencies; it is known as the McKenzie test (6). A similar effect has been suggested as part of an explanation of the glucocorticoid effect on the nasal mucosa when applying topical glucocorticoids (8).

The recently introduced ^{133}Xe wash-out method for measuring nasal mucosal blood flow has provided us with an instrument for examining glucocorticoid effects on the human nasal mucosa (2).

Aim of investigation

The aim of the present investigation was to find out whether budesonide, topically administered in the nose for 1 week, would alter the

nasal mucosal blood flow in healthy subjects free from nasal symptoms.

MATERIAL AND METHODS

The study was a double-blind cross-over randomized comparison between budesonide and placebo, and comprised 11 healthy subjects (10 males and 1 female) without any history or clinical signs of nasal disorders. Their ages ranged from 18 to 34 years (mean age 24.5). They were fully informed about the trial and gave their consent to participate. The study was approved by the Ethical Committee at the University of Lund.

Before entering the trial each subject was interviewed, and a medical examination of the nose was performed. The following parameters of the nasal condition were noted: lividity, colour, oedema and discharge. The medical examination was repeated after each treatment period; on these occasions, side effects were also noted.

Prior to the blood-flow determination there was a 1-week treatment period with either budesonide or placebo. A 2-week wash-out period was introduced before the second treatment period. The last dose was given 2 h before the blood flow measurement. The sprays were identical freon propeller canisters. No other treatment was allowed during the trial.

The nasal blood flow was determined quantitatively in the supine position by the ^{133}Xe wash-out method according to Bende et al. (2). For that purpose 0.1 ml ^{133}Xe in saline solution, containing 1–10 MBq, was injected into the mucosa of the inferior turbinate and the elimination of the isotope was followed with a scintillation detector (see Fig. 1). The blood flow was calculated from the initial slope of the first 5 min of the wash-out curve.

RESULTS

The individual values obtained from the blood-flow determinations are presented in Table 1. The mean values ($\pm$ SEM) after budesonide pretreatment were 37.0 ± 2.8 ml/min $^{-1} \times (100$ g) $^{-1}$ and after placebo pretreatment 38.4 ± 2.8

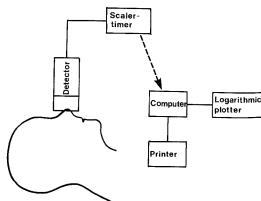


Fig. 1. Block diagram of the experimental device. All values are fed to the computer for listing blood flow on the printer and drawing the wash-out curve on the plotter.

Table 1
Blood flow (ml/min $^{-1} \times (100$ g) $^{-1}$) in the human nasal mucosa after treatment for 1 week with budesonide and placebo

Sex/Age	Budesonide	Placebo
♂ 34	37.3	28.6
♂ 29	50.0	33.3
♂ 29	37.3	45.8
♂ 29	49.1	35.3
♂ 28	32.4	48.3
♂ 21	40.8	48.8
♂ 21	42.4	40.8
♂ 21	33.0	32.8
♀ 20	22.2	33.3
♂ 20	30.3	48.3
♂ 18	32.7	26.8
Mean $\pm$ SEM	37.0 $\pm$ 2.8	38.4 $\pm$ 2.8

ml/min $^{-1} \times (100$ g) $^{-1}$. The difference is not statistically significant (paired t-test).

No serious side effects were observed. One subject had a blood-tinged secretion from the nose towards the end of the budesonide period. No specific source of bleeding could be ascertained. A few subjects experienced irritation, e.g. itching, sneezing and nasal secretion following spraying with placebo as well as with active spray. No difference was observed in the clinical examinations before and after treat-

ment with placebo; the same applies to budesonide.

DISCUSSION

Although glucocorticoids have been used in the treatment of allergic airway diseases for over 30 years, the mode of action of this treatment is still inadequately understood (9). Where the nose is concerned, topically administered glucocorticoids have been shown to be clinically effective in allergic and vasomotor rhinitis as well as in the treatment of nasal polyps (9). It has been suggested that the effect of topically administered glucocorticoids in the nose could partly be due to "vasoconstrictor" effects, similar to the effect that can be seen in the dermal McKenzie test (6).

All glucocorticoids used today have been assayed by means of this test. The lowest concentration of the glucocorticoid capable of inducing pallor in the skin under plastic occlusion indicates the vascular effect of that particular glucocorticoid. Furthermore, a rough correlation between "vasoconstrictor" potency and clinical potency in terms of anti-inflammatory potency is considered to be apparent (6).

In normal skin, the vascular effects of the glucocorticoids seem to be due to the emptying of non-pulsating vessels (15, 16). The suitability of the word "vasoconstriction" in connection with glucocorticoid activity is also debatable, as it implies active performance, but is, perhaps, merely a passive performance.

In the nose, the vascular bed can be functionally divided into two parts: the capacitance vessels, which are the vessels mainly involved in nasal congestion, and the resistance vessels which regulate the blood flow (7). Changes in the capacitance vessels have been extensively studied via indirect methods such as rhinomanometry, while changes in the resistance vessels have not been investigated in man, mainly because of methodological difficulties. The recently introduced ^{133}Xe wash-out method (2), however, reflects changes in the resistance vessels.

In a previous study where rhinomanometry was employed, the same glucocorticoid, dosage,

and period of treatment, failed to produce any changes in the nasal resistance that could be said to reflect changes in the capacitance vessels (10). In the present study, the glucocorticoid treatment did not induce any changes in the resistance vessels either. These findings suggest no "vasoconstriction" effect is responsible for the clinical effect of the glucocorticoids in the nose, at least when the present methods are used. It cannot be concluded from these studies, however, whether there are any initial or short-term changes (i.e. within 2 h) by the glucocorticoids after the given dose. Since the clinical effect is longer this is clinically irrelevant. Whether blood flow altered by disease could be normalized by the glucocorticoids cannot be confirmed in this study.

For example, a topical decongestant, oxymetazoline, caused a reduction of the nasal blood flow in the magnitude of 50% in healthy subjects, when given in normal dosage (3).

A possible explanation of the difference between the glucocorticoid effect on human skin and on the human nasal mucosa with regard to the induction of vasoconstriction might be found in the more rapid turnover of glucocorticoids in the nose as compared with the skin (5).

In order for us to be able to understand the effects of glucocorticoids in the treatment of nasal diseases, the cellular mechanisms which would appear to be involved must be studied.

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Address:

Ulf Pipkorn, M.D.
Dept. of Oto-Rhino-Laryngology
Sahlgren's Hospital
S-413 45 Göteborg
Sweden

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