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Influence of Experimental Rhinitis on the Gonadotropin Response to Intranasal Administration of Buserelin

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Summary. The influence of experimental rhinitis on the absorption of buserelin, measured as the serum luteinizing hormone (LH) response, has been investigated. A single dose of 200 μg buserelin was given to 24 healthy male volunteers after induction of experimental rhinitis with histamine and after use of a saline spray (placebo control).

Except on one occasion, when the pump-spray apparently was incorrectly operated, serum LH concentration rose after buserelin. There was no difference in the LH response between histamine-induced rhinitis and saline controls.

It was concluded that intranasal application of buserelin represents a reliable mode of application and that modification of the administration route or a change in the dosage schedule during naturally-occurring nasal inflammations, such as the common cold and allergic rhinitis, is unnecessary in patients undergoing chronic treatment with intranasal buserelin, e.g. for prostatic cancer, endometriosis, precocious puberty, and contraception.

Key words: buserelin; LHRH superagonist, histamine-induced rhinitis, pharmacokinetics, serum LH

The nonapeptide buserelin is a synthetic analogue of gonadotropin-releasing hormone (luteinizing hormone-releasing hormone, LHRH), which is 20- to 170-fold more potent than the latter, depending on the test system. Given daily in microgram amounts on a chronic basis, buserelin causes downregulation of LHRH receptors and, in turn, suppression of gonadotropin production (paradoxical superagonist effect). This forms the basis of the therapeutic use of buserelin in the treatment of endometriosis [1–3], androgen-dependent prostatic cancer [4–6], breast cancer [7, 8] and precocious puberty [9]. Inhibition of ovulation has been demonstrated [10, 11], which suggests a further possible use for buserelin in fertility control.

Oral administration is unsuitable for clinical purposes, as buserelin is a peptide and so is subject to degradation by gastrointestinal enzymes. As long-term treatment with buserelin is generally necessary for the above indications, an alternative to injection (i.v., i.m., and s.c.) is clearly desirable in terms of patient compliance. Comparison of different routes of administration has demonstrated the feasibility of the intranasal route for therapeutic purposes [12–14]. The bioavailability of buserelin applied intranasally in healthy volunteers has been shown to be 2.5% (Hoechst AG, data on file), confirming preliminary findings [15].

It is conceivable, however, that trivial afflictions, such as the common cold and hay fever, might modify the permeability of the nasal mucosa to the drug, and that drug access to the mucous membrane might be modified by nasal blockage. Thus, additional information on the effects of these conditions on drug absorption is necessary before intranasal application can be recommended for clinical use without restrictions. The aim of the present study was to investigate the influence of experimental rhinitis on the intranasal absorption of buserelin, measured as the gonadotropin response.

Subjects and Methods

Volunteers

Twenty-four healthy male volunteers were recruited for the study, mean age 24 years (range 20–29 years), mean height 182 cm (range 167–194 cm), and mean weight 75 kg (range 60–90 kg). Inclusion crite-

ria were: 1) no pathological findings on physical examination; 2) no abnormal findings in routine laboratory tests; 3) normal nasal mucosa and anatomy on inspection. Exclusion criteria were: 1) regular use of drugs; 2) alcohol abuse; 3) participation in a clinical trial during the last three months; 4) history of allergic disease; 5) history of chronic rhinitis; 6) history of gastrointestinal, hepatic or renal illness; 7) airway infection in the past 4 weeks.

All volunteers gave their informed consent to participation after being given oral and written information. The protocol was approved by the Ethical Committee of the City of Copenhagen.

Study Design

The study employed a single dose and followed a randomized cross-over, Latin square design. For each volunteer, one nostril was selected for drug administration after an anatomical examination. Each volunteer was treated with 200 μg buserelin in the selected nostril, on each of two occasions with one week between treatments. On one occasion, the drug was administered 15 min following induction of inflammation by histamine; on the other occasion, the drug was administered 15 min after saline treatment (placebo control). The two trial days were allocated according to a randomized plan. A double-blind design was attempted, but most volunteers could distinguish between histamine and saline.

On each treatment day, the experimental procedure was: 1) measurement of nasal airway resistance in the selected nostril; 2) subjective assessment of patency of the selected nostril; 3) nasal spraying with histamine or saline; 4) measurement of nasal airway resistance after 15 min; 5) buserelin administration. Step 2 was incorporated as a control for the measurement of nasal airway resistance so that if there were a significant discrepancy, the resistance could be remeasured. However, it was not found to be necessary during the study.

Histamine Administration

Inflammation in the selected nostril was produced by intranasal spraying of 0.5 mg histamine [16], using a similar metered-dose pump-spray (nebulizer) as that used for buserelin (see below). Saline was used as the placebo.

Medication

An aqueous solution of buserelin was administered using a metered-dose pump spray, which delivered 100 μg/0.09 ml per actuation; a total dose of 200 μg was administered with an interval of 5 min between sprays. The buserelin solution, 400 mosm/l, pH 5.9, was preserved with benzyl alcohol. All volunteers were instructed in use of the pump spray, and spraying was carried out under supervision of one of the investigators. The volunteer held the bottle upright, slightly bent his head over it, and began nasal inhalation before actuation of the spray. The subjects were requested to sniff gently for 20 s immediately following each spray, in order to avoid leakage of solution from the nostril, and to hold their heads in the horizontal position for 5 min and 10 min after the first and second sprays, respectively.

Determination of Nasal Airway Resistance

Using a standard method for active posterior rhinomanometry [16, 17], pressure-flow curves were obtained for the selected nostril, the other nostril being occluded with surgical tape. As described by Broms et al. [18], the standardized value of nasal airway resistance, R_2, derived from those curves is not symmetrically distributed, and is unsuitable for statistical analysis. However, the angle "v_2", corresponding to $\tan^{-1}(R_2/10)$, where R_2 is expressed in cm $H_2O \cdot s \cdot l^{-1}$, may be used for standard statistical tests [18]. The equipment used to obtain the pressure-flow curves was calibrated to yield v_2 directly.

Gonadotropin Response

Serum luteinizing hormone (LH) concentrations were determined by radioimmunoassay, using a commercially available kit (RIA-gnost hLH-Tachisorb, Behringwerke AG, Marburg, FRG) in blood samples taken immediately before nasal buserelin administration and after 30 min and 1, 1.5, 2, 2.5, 3, 4, 5 and 6 h.

Tolerance

Any adverse reactions observed by the investigator or reported by the subjects following buserelin treatment were recorded for subsequent assessment. Blood samples for routine safety tests (haematology, serum clinical chemistry and urinalysis) were taken before the study and after its completion.

Statistical Analysis

Individual maximum LH response (LH-C_{max}) and time to reach LH-C_{max} (LH-t_{max}), following buserelin administration were obtained directly from the

Table 1. Effect of saline and histamine administration on nasal airway resistance (median values; $n=23$)

Treatment	Nasal airway resistance, R_2 (cm $H_2O \cdot s \cdot l^{-1}$)[a]	
	Before treatment	After treatment
Saline	5.4	4.7
Histamine	4.2	10.3

NS (Saline vs. Histamine); ★ (Saline vs. Histamine); NS (Before vs. After, Saline); ★ (Before vs. After, Histamine)

[a] Statistical analysis was performed on v_2, i.e. $\tan^{-1}(R_2/10)$ (see Methods); NS not significant; ★ $p<0.05$

Table 2. Pharmacokinetics of serum luteinizing hormone release following nasal administration of buserelin (median values; $n=23$)

	Control	Experimental rhinitis[a]
LH-serum baseline (mU/ml)	6.10	5.60
LH-C_{max} (mU/ml)	17.70	19.80
t_{max} (h)	3.00	3.00
LH-AUC (0-6) (mU·h/ml)	81.80	84.02

[a] Differences between control and experimental rhinitis were not significant

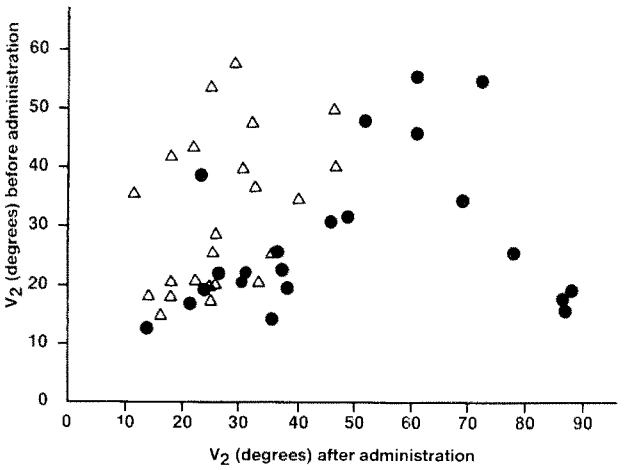

Fig. 1. Individual values of nasal airway resistance, expressed as v_2 (see Methods), before and after intranasal saline (△) and histamine (●)

serum LH concentrations by subtracting the corresponding basal serum LH levels. Areas under the serum LH concentration-time curves to 6 h (LH-AUC (0-6)) were calculated using the trapezoidal rule. Differences between the values of LH-C_{max}, LH-t_{max} and LH-AUC (0-6) following the two treatments (histamine-induced rhinitis and placebo) were tested for significance ($p<0.05$) using the Wilcoxon test for paired samples. Values of nasal airway resistance, v_2, before and after administration of histamine or saline were compared within each treatment as well as between treatments, also using the paired Wilcoxon test ($p<0.05$).

Results

Effect of Histamine on Nasal Airway Resistance

Nasal airway resistance before histamine administration (Table 1) and the baseline serum LH concentrations (Table 2) were comparable on the two treatment days.

Individual values of v_2 obtained before and after saline and histamine administration, respectively, are shown graphically in Fig. 1. The increase in nasal airway resistance following histamine administration is revealed by the shift towards the lower part of the figure of the data points as compared to the values after saline administration. Histamine administration significantly increased nasal airway resistance (Table 1), but in no case was the nose completely blocked.

In three subjects with near-complete blockage ($v_2>80°$, i.e. nasal airway resistance >56.7 cm $H_2O \cdot s \cdot l^{-1}$), buserelin medication was postponed until the nasal airway resistance had dropped below this value. Saline administration did not significantly affect the nasal airway resistance.

Effect of Buserelin on LH Concentrations

Of 48 intranasal applications of buserelin, 47 led to LH release. The single failure was thought to be due to incorrect operation of the pump spray. This volunteer had shown a hormonal response within the distribution range for the entire group on the other treatment day (histamine pretreatment). Data from him were excluded from the analysis.

The individual and median serum LH concentrations at various times after buserelin treatment are shown in Fig. 2, and Table 2 gives the corresponding values for the various pharmacokinetic parameters.

Serum LH concentrations rose steeply during the first 30 min after spraying, reaching a maximum at 3-4 h followed by a gradual decline.

There were no statistically significant differences between the histamine-induced rhinitis and control tests in any of the pharmacokinetic parameters describing LH release. Although there was no significant difference between the standard deviations of

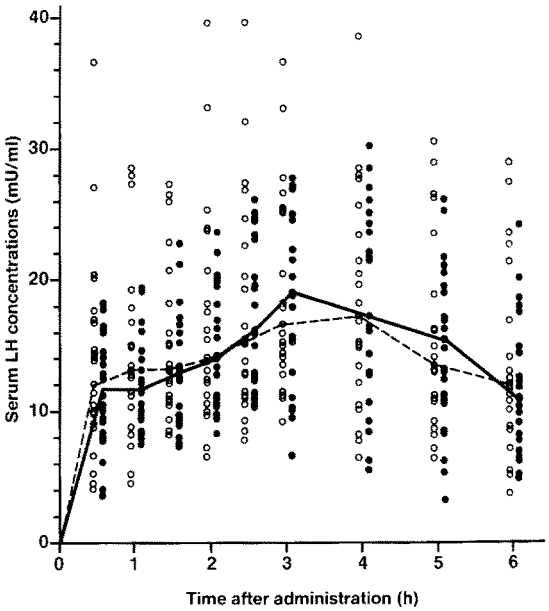

Fig. 2. Individual and median serum concentrations (mU/ml) of luteinizing hormone (LH) at various times following intranasal buserelin; saline control (O--O--O); histamine-induced rhinitis (●—●—●). Values are corrected for baseline; six data points at high LH concentrations (>40 mU/ml) are not shown

LH-AUC (0-6) following the two treatments, there was a tendency for greater scatter in the data after saline than in rhinitis: i.e. interindividual variation in this parameter was reduced after histamine administration (Fig. 2).

Tolerability

No clinically relevant changes were noted in haematological, biochemical or urine analyses. Following saline and buserelin administration, one subject developed a slight headache, not considered related to medication. Following the histamine and buserelin administration, one subject suffered from nasal stenosis and coughing (24 h after dosing), one from secretion from the nose (2-5 h after dosing), and one from a mild headache and moderate fatigue (6-14 h after dosing). All the side effects were considered most probably to have been late effects of the histamine challenge.

Discussion

The present investigation revealed that the serum LH response to 200 μg buserelin, administered by nasal insufflation using a metered-dose pump spray, was not affected by histamine-induced rhinitis as compared to a saline control. The response was assessed as a series of pharmacokinetic variables (baseline values, C_{max}, t_{max}, AUC (0-6)).

The premedication conditions were comparable on both treatment days. No significant differences were found either in serum LH levels or nasal function variables before the administration of buserelin. As expected, the histamine spray induced a significant increase in nasal airway resistance, which corresponded to the self-assessed score for nasal blockage. On the other hand, neither objective nor subjective measurement of the air passage was influenced by insufflation of placebo.

The lack of a difference in LH pharmacokinetics following histamine and saline pretreatment means that the same fraction of the administered dose of buserelin was absorbed by the inflamed and normal nasal mucosa. Histamine-induced inflammation of the nasal mucosa is known to increase epithelial permeability to albumin and other substances (unpublished results). In the present study, this would have led to higher C_{max} and AUC (0-6) for buserelin after histamine pretreatment. Since this was not observed, if indeed buserelin absorption were increased following histamine-induced inflammation, other concomitant, physiological changes must have counterbalanced the increased drug absorption.

The interaction between increased absorption on the one hand and factors such as airway narrowing and increased nasal secretion (both impeding drug access to the nasal mucosa) on the other, might explain the similar LH response after the histamine and saline pretreatments. Alternatively, it is possible that neither drug access to nor absorption by the nasal mucosa was influenced by histamine-induced rhinitis.

The fact that the single failure of response following buserlin administration occurred following saline rather than histamine pretreatment indicates that on this occasion, the volunteer must have received a low dose of buserelin, presumably due to incorrect operation of the pump spray.

The results of the safety tests showed that a single dose of the buserelin spray was well tolerated. All the side-effects were of minor importance, and were probably due to the histamine administration.

It is likely that the present results, in which the histamine-induced nasal inflammation was quite severe, can be extended to include naturally-occurring nasal inflammations, such as the common cold and allergic rhinitis. No modification of the administration route or change in the dosage schedule would be necessary in patients on chronic treatment with intranasal buserelin, e.g. for prostatic cancer, endometriosis, precocious puberty, or contraception.

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