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Vasomotor rhinitis and the systemic absorption of ipratropium bromide

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SUMMARY

Plasma concentrations of nasally administered ipratropium bromide were analyzed in 10 subjects suffering from severe vasomotor rhinitis and in 10 age-sex matched control subjects. The rate of salivary secretion and heart rate were monitored in order to measure systemic anticholinergic effects. A total dose of 360 μg of ipratropium bromide (60 μg into each nostril, repeated twice at 15 min intervals) were administered nasally to the subjects in randomized order. Ipratropium bromide was rapidly absorbed from the nasal mucosa into the systemic circulation in both groups. The peak plasma concentrations were detected within 10 min after the last drug administration. The peak concentrations were about 50% higher (380± 153 pg/ml) in patients than in control subjects (245± 134 pg/ml). The AUCs/0-15 min (1970± 1140 pg/ml× min) in patients were about 100% higher than in the control subjects (960± 560 pg/ml× min). During the experiment there was a small decrease in the heart rate (8 bpm) and salivary secretion (10%) in both groups. In conclusion, the vasomotor rhinitis increases the systemic absorption of nasally administered ipratropium bromide, but the small increase in the absorption is not likely to have any clinical consequences.

INTRODUCTION

Ipratropium bromide, a quaternary derivative of N-isopropyl atropine was originally introduced as a bronchodilator administered from metered-dose aerosols (Poppius et al., 1973). Because of its high topical anticholinergic activity nasally administered ipratropium bromide has been successfully used in the treatment of hypersecretory nasal disorders (Borum et al., 1981; Malmberg et al., 1983). In healthy volunteers negligible amounts of ipratropium bromide were absorbed from the nasal mucosa into the systemic circulation consistent with lack of any systemic anticholinergic effect of the drug (Laurikainen et al., 1988).

Because ipratropium bromide is used in patients with swelling of the nasal

mucosa, we were interested to evaluate how rhinitis influences the systemic absorption of the drug. The changes of the mucosa in hypersecretory disorders are likely to increase the permeability of the epithelium, whereas the secretions on the mucosa are likely to act as an barrier for the absorption. We administered ipratropium bromide nasally to 10 patients suffering from severe vasomotor rhinitis and to 10 age-sex matched healthy control subjects. Ipratropium bromide concentrations in plasma, heart rate and salivary secretion were monitored up to 90 min following the drug administration in order to estimate the effects of vasomotor rhinitis on the systemic absorption and action of nasally administered ipratropium bromide.

MATERIALS AND METHODS

Twenty subjects, ten patients suffering from hypersecretory rhinitis and ten healthy subjects participated in the study after their informed consent. The study protocol was approved by The Ethical Committee of Turku University Hospital.

Patient group

Five male and five female patients (mean $\pm$ s.d., age 43.1 $\pm$ 12.3 years, weight 69.5 $\pm$ 11.6 kg) suffering from severe vasomotor rhinitis and not from other diseases were included in this group. The duration of the previous treatment of the disease with various drugs had lasted at least for a year before the patients were admitted to the Department of Otorhinolaryngology at Turku University. In spite of the treatment, patients had suffered daily for hours from nasal symptoms such as rhinorrhea and stuffed nose. Before administering ipratropium bromide the patients had a drug-free period of at least one month. The skin prick tests for allergy were negative. There were no polyps or abnormalities in the anatomy of the nose of the patients. The rhinological status was re-evaluated by a rhinologist immediately before beginning of the experiment.

Control group

Five healthy females and five healthy males (mean $\pm$ s.d., age 36.5 $\pm$ 15.6 years, mean weight 73.9 $\pm$ 12.2 kg) were included in the control group. The subjects had no history of hypersecretory nasal symptoms and they have never had long-lasting (over two weeks) medication for any nasal disease. The subjects were free from nasal symptoms. There were no abnormalities in the anatomy of the nose of the subjects. They had no medication for at least a month for any disease. The rhinological status was re-evaluated by a rhinologist immediately before administration of ipratropium bromide. No mucosal swelling was observed in any of the subjects at the time of experiment.

Drugs

Ipratropium bromide (20 μg/dose, Atrovent Nasal®, Boehringer Ingelheim International, Ingelheim am Rhein, Fed. Rep. of Germany).

Experiment

The rhinological and general status of all subjects participating in the study were examined at 1.00 p.m. at the Department of Otorhinolaryngology at the University of Turku. Subjects fulfilling the inclusion criteria (patient group or control group) were chosen and admitted in randomized order to the Department of Clinical Pharmacology for drug absorption studies. The personnel at the Department of Clinical Pharmacology was unaware about the group each subject belonged to. At 2.00 p.m. the subjects were asked to lay down, polyethylene cannulas were inserted in into a antecubital vein and maintained patent with a dilute heparin. The subjects were supine for the duration of the study. The first blood samples and recordings were taken after a minimum of 15 min had elapsed since the completion of these preparations. As soon as the blood sampling and recordings for the time 0 (zero) were completed ipratropium bromide (Atrovent Nasal®) was administered three times into each nostril by a standardized manner from the aerosol canister. Thereafter, two series of three puffs into each nostril were repeated twice at 15 min interval. The total amount of ipratropium bromide administered was accordingly 18 puffs corresponding a dose of 360 μg in 30 min.

Recordings

Heart rate was monitored by an automatic EKG device (Portable patient monitor, Nihon Kohden Corp., Tokyo, Japan). The average heart rate (bpm, 30s recording) at the time of each drug administration and 15, 30, 60, and 90 min after the last dose was used in the statistical analysis. Basal (non-stimulated) salivary secretion (g/min) was measured using three pre-weighed dental cotton rolls, placed at the orifice of parotid ducts and sublingually before the drug administration and 15, 30, 60, and 90 min after the last dose.

Measurement of ipratropium bromide in plasma

The assay was a modification of the assay described for ipratropium bromide by Ensinger et al. (1987). Blood for the radioreceptor assay (RRA) was sampled in tubes containing K_2EDTA as anticoagulant. One millilitre of plasma sample was mixed with 100 μl of 0.01 M natriumpicrate solution. Ipratropium bromide was extracted into 4 ml of dichloroethane, after which two 2 ml aliquots were lyophylized in polypropylene tubes. The lyophylized samples were equilibriuted with 0.5 nM tritiated N-methyl-scopolamine (NMS s.a. 80 Ci/mmol, New England Nuclear, Boston, USA) and with 0.3 nM muscarinic cholinergic receptors obtained from rat brain. The ipratropium bromide in the unknown samples was

determined against a calibration curve from plasma standards of ipratropium bromide prepared in drug-free plasma. The detection limit of the RRA for ipratropium bromide in plasma was 50 pg/ml. The intra- and interassay coefficient of variations (CV) for 50 pg/ml and 500 pg/ml standards were within 10%.

Data analysis

The pharmacokinetic parameters were computed by using SIPHAR programs (SIMED S.A., Poitiers, France). Analysis of variance (factors ipratropium bromide concentration, heart rate and salivary secretion) and the statistical significance of the differences between the groups and time were computed by univariate and multivariate repeated measures of analysis using Systat program (Systat, Inc., Illinois, USA). The statistical significance of the differences between the groups in factors AUC/0–15 min, AUC/0–90 min, CMAX, and time to peak-value was calculated by t-test using Systat program.

RESULTS

Ipratropium bromide was rapidly absorbed from the nasal mucosa into the systemic circulation. The time required to reach the concentration maximum (CMAX), the time-to-peak value, was similar in the patient group (39.5 ± 23.8 min, mean $\pm$ s.d.) and in the control group (34.5 ± 26.5 min). The CMAX of ipratropium bromide was about 50% higher in the patients (380 ± 153 pg/ml, mean $\pm$ s.d.) than in the control subjects (245 ± 134 pg/ml). The differences in time-to-peak and CMAX values between the groups did not reach statistical significance, $p = 0.1$ and $p = 0.7$, respectively. The area under the absorption curve (AUC)/0–15 min was significantly higher in the patient group than in the control group, $p = 0.02$, which was due to the high difference in ipratropium bromide concentrations between the groups at the beginning of the experiment. The ipratropium bromide concentrations in patients and control subjects following the drug administration are presented in Figure 1. The pharmacokinetic parameters are presented in Table 1. The decrease in heart rate (about 8 bpm) and salivary secretion (10%) during the experiment was similar in both groups.

DISCUSSION

Radioreceptor assays can be used for measuring pg/ml-levels of anticholingergic drugs in plasma (Lahdes et al., 1988; Iisalo et al., 1988; Kaila et al., 1989). The low levels of ipratropium bromide in plasma following its intranasal administration were recently measured using a radioreceptor assay and the amount of its systemic absorption was estimated (Laurikainen et al., 1988). In the literature there are actually no data available concerning the effects of rhinitis on the systemic drug absorption, although many drugs are administered intranasally to

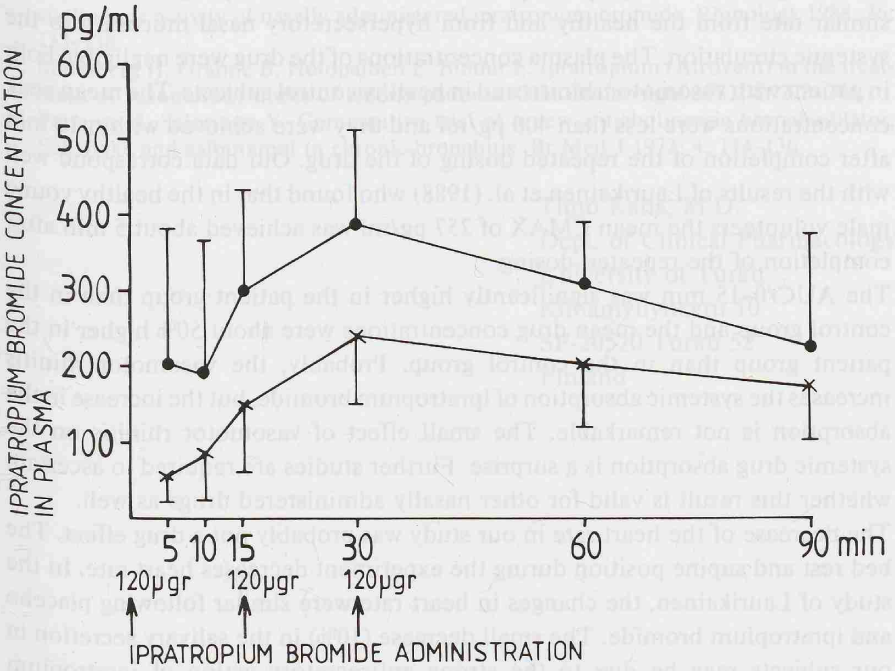

Figure 1. Mean ipratropium bromide concentration in plasma pg/ml, expressed as mean with standard deviation (bar). Patients with hypersecretory rhinitis are denoted with ● and healthy subjects with ×. Three puffs of ipratropium bromide to each nostril (Atrovent Nasal®) were administered three times with 15 min interval corresponding a total dose of 360 µg.

Table 1. Pharmacokinetic parameters characterizing the systemic absorption of nasally administered ipratropium bromide.

	AUC/0–15 min pg/ml × min	AUC/0–90 min pg/ml × min	CMAX pg/ml	time-to-peak min
patient group				
mean	1970	22700	380	39.5
s.d.	1140	8900	153	23.8
control group				
mean	960	14400	245	34.5
s.d.	560	6400	134	26.5

Only the difference in AUC/0-15 min between the groups is statistically significant, $p = 0.02$.

patients with hypersecretory nasal disorders. This might be due to the lack of methods sensitive enough for measuring low drug concentrations after their nasal application.

According to our study ipratropium bromide absorbs rapidly and at almost similar rate from the healthy and from hypersecretory nasal mucosa into the systemic circulation. The plasma concentrations of the drug were negligible both in patient with vasomotor rhinitis and in healthy control subjects. The mean peak concentrations were less than 400 pg/ml and they were achieved within 10 min after completion of the repeated dosing of the drug. Our data correspond well with the results of Laurikainen et al. (1988) who found that in the healthy young male volunteers the mean CMAX of 257 pg/ml was achieved about 5 min after completion of the repeated dosing.

The AUC/0–15 min was significantly higher in the patient group than in the control group and the mean drug concentrations were about 50% higher in the patient group than in the control group. Probably, the vasomotor rhinitis increases the systemic absorption of ipratropium bromide, but the increase in the absorption is not remarkable. The small effect of vasomotor rhinitis on the systemic drug absorption is a surprise. Further studies are required to ascertain whether this result is valid for other nasally administered drugs as well.

The decrease of the heart rate in our study was probably not a drug effect. The bed rest and supine position during the experiment decreases heart rate. In the study of Laurikainen, the changes in heart rate were similar following placebo and ipratropium bromide. The small decrease (10%) in the salivary secretion in our subjects may be due to the strong antisecretory action of ipratropium bromide (Borum, 1978). Laurikainen using a dose of 240 μg did not notice any changes in the salivary secretion. The total dose of ipratropium bromide in our study was 360 μg. It is about nine fold to that recommended a single dose for vasomotor rhinitis. Obviously, no decrease in the salivary secretion is to be waited by usual dosing of the drug with vasomotor rhinitis.

In conclusion, the vasomotor rhinitis increases the systemic absorption of nasally administered ipratropium bromide. The small increase in the absorption is not likely to have any consequences concerning the clinical use of the drug.

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