Rhinology, 26, 133-138, 1988

Evaluation of the systemic anticholinergic activity of nasally administered ipratropium bromide

Esa Laurikainen, Markku Koulu, Tima Kaila, Mika Scheinin and Esko Isalo, Turku, Finland

SUMMARY

Plasma concentrations of nasally inhaled ipratropium bromide were analyzed in eight healthy volunteers by using a sensitive radioreceptor assay (RRA). The rate of saliva secretion, heart rate and changes in visual accommodation were quantitated in order to measure possible systemic anticholinergic drug effects. 240 μg of ipratropium bromide (40 μg each nostril, repeated twice at 15 min intervals) were inhaled nasally in a double blind, randomized, placebo-controlled experiment. Ipratropium bromide absorbed fast, and peak plasma concentrations of the drug (257 ± 55 pg/ml) were detected as soon as 5 min after the last inhalation (at 35 min from the beginning). The plasma levels of ipratropium bromide decreased rapidly, being only 86 ± 7 pg/ml one hour after the last inhalation. These low concentrations of ipratropium bromide indicate that only a small portion of it absorbs after nasal application, which is consistent with the lack of any systemic anticholinergic drug effects in our subjects. It is concluded that nasally applied ipratropium bromide is not likely to cause systemic anticholinergic side-effects, even in doses exceeding the therapeutic recommendations.

INTRODUCTION

Ipratropium bromide has been successfully used in the treatment of hypersecretory nasal disorders. It is a quaternary derivative of N-isopropyl noratropine, and was first used as an inhaled bronchodilator administered from metered-dose aerosols (Poppius et al., 1973). The high topical activity of ipratropium bromide and its very favourable clinical effects on vasomotor rhinitis (Borum, 1978; Jokinen et al., 1983), together with its relatively high therapeutic ratio (Groth et al., 1983; Massey and Gotz, 1983), have made nasally administered ipratropium bromide popular in the treatment of this disease.

Pharmacokinetic studies have demonstrated a low systemic absorption of ipratropium bromide after oral administration or inhalation to the lungs (Adlung et al., 1976; Ensing et al., 1986), which is probably due to its quaternary structure. Also clinically, relatively few systemic side-effects have been reported (Groth

et al., 1983; Jokinen et al., 1983; Massey and Gotz, 1985), in spite of the high topical anticholinergic activity of the drug. Transient dryness of the mouth has, however, been reported in up to 15% of patients receiving ipratropium bromide for chronic obstructive lung disease (Ulmer, 1975).

Although the absorption of orally inhaled ipratropium bromide seems to be limited, its systemic bioavailability after nasal inhalation may be different; the absorption area of nasal epithelium is large and the mucosa is highly vascularized resulting in efficient absorption of compounds of various chemical nature. Since no data on the pharmacokinetics of nasally inhaled ipratropium bromide existed, the concentrations of ipratropium bromide in plasma and systemic anticholinergic drug effects after nasal inhalation were investigated in healthy volunteers using a sensitive and specific radioreceptor assay (RRA) (Aaltonen et al., 1984; Iisalo and Aaltonen, 1984).

MATERIALS AND METHODS

Subjects

Eight healthy, non-smoking male volunteers (ages 23-32 years) participated in the study after informed consents.

Drugs

Ipratropium bromide (20 µg/dose) (Atrovent Nasal®) and placebo aerosols with similar appearance, containing the carrier gas only, were coded and supplied by Boehringer Ingelheim Ltd., West-Germany.

Study outline

The study was a double-blind, placebo-controlled experiment. Each of the subjects received nasally both aerosols in a randomized order at one week intervals. The experiments were carried out starting at 3.00 p.m., the subjects having fasted for four hours before the tests. After arriving to the clinical pharmacology laboratory, the subjects were asked to lay down, and a polyethylene cannula was inserted into a cubital vein and maintained patent with a dilute solution of heparin. The subjects remained supine for the duration of the sessions. 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 time 0 (zero) were completed, the subjects sat up and took two inhalations into each nostril from the appropriate aerosol canister. After these four puffs, the subjects lay down again. Thereafter, the series of two puffs into both nostrils was repeated twice, at 15 min intervals (i.e. 12 puffs or 240 µg of ipratropium bromide in 30 min).

Recordings

To objectively measure anticholinergic drug effects, heart rates, near vision distances and saliva secretion rates were quantitated. In addition, subjective side-effects were inquired and recorded at each blood sampling time.

Heart rate was measured by wrist palpitation (30 sec) at 0 (after at least 15 min of bed rest), 15, 30, 35, 40, 45, 60, 90 and 120 min.

Basal (non-stimulated) saliva secretion was measured using three pre-weighed dental cotton rolls, placed at the orifices of the parotid ducts and sublingually for 2 min at 0 (zero), 15, 30, 45, 60, 90 and 120 min.

Visual accommodation capacity was quantitated by measuring the nearest distance where the subject was able to read a standard text (=near vision distance). Recordings were taken at 0, 15, 30, 35, 40, 45, 60, 90 and 120 min.

Radioreceptor assay (RRA) of ipratropium bromide

Blood for RRA was sampled into chilled tubes containing K_2EDTA as anti-coagulant, immediately placed on ice, and centrifuged in a refrigerated centrifuge within 30 min of collection. Concentrations of ipratropium bromide in plasma were analyzed at 0, 15, 30, 35, 40, 45, 60, 90 and 120 min after the administration of the drug. A modification of the RRA method of Aaltonen et al. (1984) was used. As tracer we used N-methyl-^{3}H-atropine. The assays were carried out in duplicate. The detection limit of the RRA for ipratropium bromide was 50 pg/ml in plasma. The intra-assay coefficient of variation (CV) was 2% at concentrations of 50 pg/ml and 500 pg/ml of ipratropium bromide, and the interassay variation 3% at 50 pg/ml and 6% at 500 pg/ml, respectively.

Statistical methods

Analysis of variance (ANOVA), with two within-factors (treatment, time) was computed with Systat® programs (Systat, Inc., Illinois, U.S.A.).

RESULTS

Ipratropium bromide was well tolerated. No subjective side-effects were reported during the study. The absorption of ipratropium bromide after nasal inhalation was fast, since peak concentrations in plasma were found at 35 min after the first administration of the drug. Only a small proportion of the drug was absorbed, however, as indicated by the low levels of ipratropium bromide in plasma, the mean ($\pm$SEM) peak levels being only 257 ± 55 pg/ml. Plasma concentrations of ipratropium bromide decreased rapidly, being under detection limit (50 pg/ml) in half of the subjects at 120 min (Table 1).

There were no indications of systemic antimuscarinic drug effects. Ipratropium bromide did not affect the rate of saliva secretion, heart rate or near vision distance in the subjects, when compared to placebo treatment (Table 2).

Table 1. The concentrations of ipratropium bromide in plasma of eight volunteers after nasal inhalation of 4 puffs, repeated three times in 30 min (i.e. 240 µg total dose). ND = not detectable (below detection limit of 50 pg/ml). The values are pg/ml of ipratropium bromide.

	time min								
	0	15	30	35	40	45	60	90	120
1	ND	90	60	140	110	115	90	90	60
2	ND	ND	ND	90	60	ND	ND	ND	ND
3	ND	ND	75	230	140	110	95	ND	ND
4	ND	ND	150	300	270	200	150	100	100
5	ND	150	180	515	200	400	150	80	60
6	ND	80	150	70	60	60	ND	ND	ND
7	ND	90	135	170	320	130	95	100	100
8	ND	90	100	460	180	170	70	60	ND
Mean	-	105	111	257	169	169	101	86	80
SEM	-	15	17	55	33	42	14	7	12
n		4	7	8	8	7	7	5	4

Table 2. The saliva secretion, heart rate and near vision distance after nasal inhalations of placebo (P) and ipratropium bromide (I) in eight volunteers. The values are means ± SEM. ANOVA did not reveal any statistically significant differences between the two treatments.

time	saliva secretion g/2 min		heart rate beats/min		near vision distance cm	
	P	I	P	I	P	I
0	1.393 ± 0.286	1.731 ± 0.532	70.9 ± 3.0	66.5 ± 4.5	10.1 ± 0.7	10.0 ± 0.8
15	1.257 ± 0.302	1.749 ± 0.480	66.8 ± 3.4	63.3 ± 3.6	10.1 ± 0.9	9.5 ± 0.8
30	1.442 ± 0.301	1.924 ± 0.450	64.6 ± 3.6	62.8 ± 3.5	10.0 ± 0.9	9.9 ± 0.8
35	not done	not done	65.0 ± 3.0	62.0 ± 3.3	10.3 ± 1.0	9.9 ± 0.9
40	not done	not done	63.6 ± 2.2	60.4 ± 2.6	10.3 ± 1.2	10.1 ± 1.1
45	1.471 ± 0.344	1.422 ± 0.393	64.6 ± 2.8	60.3 ± 2.7	10.5 ± 0.9	10.0 ± 1.1
60	1.244 ± 0.265	1.638 ± 0.385	66.5 ± 3.3	61.3 ± 2.8	10.3 ± 1.0	10.0 ± 1.1
90	1.415 ± 0.351	1.360 ± 0.348	64.6 ± 3.1	62.0 ± 4.1	10.2 ± 0.9	9.5 ± 0.9
120	1.708 ± 0.458	1.387 ± 0.281	66.3 ± 3.0	62.3 ± 2.5	9.9 ± 0.9	9.6 ± 1.0

DISCUSSION

The present study demonstrates that nasally inhaled ipratropium bromide is well tolerated even in doses exceeding usual therapeutic recommendations. By using a sensitive RRA assay for ipratropium bromide, its plasma concentrations could be quantitated. These measurements revealed that ipratropium bromide is absorbed from the nasal mucosa; the absorption was fast resulting in peak plasma concentrations of the drug only 5 min after the completion of repeated dosing. Only a small amount of ipratropium bromide was, however, absorbed. This is consistent with the lack of any antimuscarinic drug effects in our volunteers. Because of problems in analyzing low plasma concentrations of ipratropium

bromide, only limited data on its pharmacokinetic properties exist. After oral inhalation of 555 µg of radiolabeled ipratropium bromide, a peak plasma concentration of 60 pg/ml was achieved three hours after the administration of the drug (Adlung et al., 1976). The time course of the plasma concentrations after orally inhaled ipratropium bromide was found to be similar to that after oral administration of the drug (Adlung et al., 1976); it was suggested that most of the orally inhaled ipratropium bromide is deposited on the mucosa of the mouth and upper airways, and is subsequently swallowed (Massey and Gotz, 1985). It should be noted that these conclusions are based on studies on radiolabeled ipratropium bromide. In a recent study, where RRA was used, the systemic bioavailability of ipratropium bromide inhaled to the lungs was estimated to be 7%, and that of an oral dose only 3% (Ensing et al., 1986). Plasma levels exceeding 1 ng/ml (after intravenous administration of 2 mg or oral doses of 20 mg of the drug) were related to marked increases in heart rate (Ensing et al., 1986).

The results of the present investigation suggest that the absorption of nasally inhaled ipratropium bromide may be greater and faster than that of orally inhaled drug. It is likely that nasally applied ipratropium bromide is absorbed mainly from the nasal mucosa. The peak concentrations we found in the present study are about four times as high as those reported after oral inhalation of about the twice of the present dose (Adlung et al., 1976). The proportionally greater concentrations of ipratropium bromide after nasal application are most likely due to the high vascularity of the nasal mucosa and the large absorption area. Nevertheless, the concentrations of ipratropium bromide in plasma remained very low throughout the study. Thus, only negligible amounts of ipratropium bromide appear to be absorbed after nasal inhalation.

We conclude that with the recommended doses (2 puffs into both nostrils 3–4 times/day) intranasally used ipratropium bromide is likely to be devoid of systemic side-effects even in patients with such diseases as prostatic hypertrophy or glaucoma.

ZUSAMMENFASSUNG

Nach nasaler Inhalation von Ipratropiumbromid wurden bei acht gesunden Freiwilligen die Plasmakonzentrationen mit einem empfindlichen Radiorezeptor-Test (RRA) analysiert. Die Menge der Speichelsekretion, die Herzfrequenz und Veränderungen der Akkommodation wurden bestimmt, um mögliche systemische anticholinerge Wirkungen zu erfassen. 240 µg Ipratropiumbromid (40 µg in jedes Nasenloch und in Intervallen von 15 Min. wiederholt) wurden nasal in einer randomisierten Doppelblindstudie inhaliert. Ipratropiumbromid wird rasch absorbiert, und Plasmaspitzenkonzentrationen von 257 ± 55 pg/ml wurden schon 5 Minuten nach der letzten Inhalation (35 Min. nach dem Beginn) gemessen. Die Plasmaspiegel des Ipratropiumbromid sanken rasch und waren

eine Stunde nach der letzten Inhalation nur noch 86±7 pg/ml. Diese geringen Konzentrationen von Ipratropiumbromid weisen darauf hin, daß nur ein kleiner Teil nach nasaler Applikation absorbiert wird, was gut übereinstimmt mit der Beobachtung, daß keine systemischen Nebenwirkungen bei unseren Probanden festgestellt wurden.

Es wird daher gefolgert, daß nasal appliziertes Ipratropiumbromid wahrscheinlich keine systemischen antcholinergen Nebenwirkungen hervorruft, auch nicht nach einer Dosierung, die die therapeutisch empfohlene überschreitet.

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Dr. Esa Laurikainen
Dept. of Otorhinolaryngology
Turku University Hospital
SF-20520 Turku
Finland