

Product characteristics and pharmacokinetics of intranasal ipratropium bromide

Chester C. Wood, MD,^a Philip Fireman, MD,^b Jay Grossman, MD,^c
Margaret Wecker, PhD,^a and Thomas MacGregor, PhD^a Ridgefield, Conn.,
Pittsburgh, Pa., and Tucson, Ariz.

The in vivo absorption potential of ipratropium bromide nasal spray was evaluated in studies involving healthy volunteers (0.03%, 0.06%, and 0.12% dosage strengths) and patients with perennial rhinitis (0.03% and 0.06%) and the common cold (0.06%). The dose used was two sprays per nostril, corresponding to a total dose of 84 µg, 168 µg, and 336 µg for the three dosage strengths. These studies indicate that 10% or less of active drug is absorbed systemically after nasal administration based on the amount of unchanged drug excreted in urine in a 24-hour interval. In most instances, the plasma drug concentrations were undetectable. In none of these studies did plasma ipratropium concentrations reach a level where systemic anticholinergic effects are known to occur. (J ALLERGY CLIN IMMUNOL 1995; 95:1111-6.)

Key words: Ipratropium, nasal spray, pharmacokinetics, rhinitis, common cold

The medicinal properties of atropine and related alkaloids have been known for centuries, but it is only in the past 25 years that a serious interest in anticholinergic agents has been revived among clinicians. There are two reasons for this renewed interest. We now have a better understanding of the cholinergic nervous system and its role in the pathophysiology of such disease states as chronic obstructive pulmonary disease and rhinitis,¹ and this improved understanding has coincided with the development of ipratropium bromide and other synthetic anticholinergic agents that are not appreciably absorbed and cause few adverse effects.²

Ipratropium is a quaternary ammonium compound structurally designed to minimally cross the nasal epithelial and gastrointestinal membranes and the blood-brain barrier.³ Its partition coefficient is 15-fold lower than that of atropine. Ipratropium bromide is widely used in an aerosol formulation to relieve the bronchospasm associated with chronic obstructive pulmonary disease. More recently, the compound's anticholinergic properties, topical po-

tency, water solubility, and low absorption potential have led to the development of a new aqueous nasal spray for the control of rhinorrhea (Atrovent Nasal Spray [ipratropium bromide], Boehringer Ingelheim Pharmaceuticals, Ridgefield, Conn.).

Ipratropium bromide nasal spray consists of active drug dissolved in an isotonic aqueous solution. It has been adjusted to a pH of 4.7 to make it compatible with the nasal mucosa. The spray contains the microbial preservatives ethylenediaminetetraacetic acid and benzalkonium chloride, which are recognized in the compendium. The spray is dispensed as a fine droplet mist by means of a manual pump and is administered at a volume of 70 µl per actuation; each dose contains 21 or 42 µg of ipratropium bromide corresponding to dosage strengths of 0.03% and 0.06%, respectively.

The pump system contains no chlorofluorocarbons and allows for more uniform delivery than an aerosol. There are two basic elements to the pump system: a metering mechanism that provides a uniform dose per actuation and a check valve to prevent biological fluids from contaminating the medication reservoir. The pump is fully primed at the time of manufacture and remains primed after actuation by means of the check valve; a single spray delivers the full dose each time the pump is used. The integrity of the system is thus maintained during long-term use.

Ipratropium bromide remains positively charged

From Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Conn.,^a Pittsburgh, Pa.,^b and Tucson, Ariz.,^c

Reprint requests: Chester C. Wood, MD, Boehringer Ingelheim Pharmaceuticals, Inc., P.O. Box 368, Ridgefield, CT 06877-0368.

Copyright © 1995 by Mosby-Year Book, Inc.

0091-6749/95 \$3.00 + 0 1/0/63460

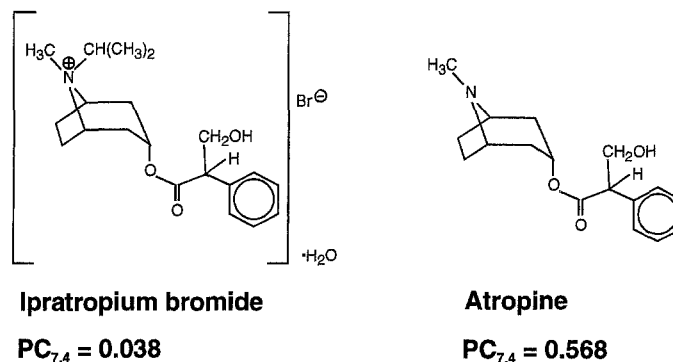


FIG. 1. Schematic representation of the chemical structures of ipratropium bromide and atropine. PC_{7.4} is the octanol-buffer partition coefficient at pH 7.4.

at all pH values and is freely soluble in water (Fig. 1). It is less than 10% protein bound; the drug delivered in any given dose is readily available for effect at the receptor. When systemically absorbed, ipratropium has an erythrocyte to plasma ratio of 0.6. Plasma drug assays are therefore indicative of total blood concentrations. Incubation studies demonstrate that ipratropium remains stable in nasal mucosal excretions for more than 4 hours. The stability of the drug at the pH value of the nasal mucosa is approximately 2 years; drug clearance from nasal passages, therefore, is primarily due to mucociliary mechanisms.

A pharmacokinetic comparison with intravenous administration demonstrated that less than 10% of ipratropium is absorbed when it is administered in various extravascular formulations.⁴ Because it has an organic ion, the drug is distributed to the organs of excretion and does not cross the blood-brain barrier.⁵ It is rapidly metabolized by ester hydrolysis to tropic acid (one of the main ingredients of soft drinks) and *N*-isopropylmethyl nortropanium.⁶ Both metabolites are inactive.⁷ The drug is rapidly excreted by the kidneys at about six times the glomerular filtration rate.⁴

To establish a pharmacokinetic profile for the use of ipratropium bromide nasal spray, we studied its absorption characteristics in four clinical trials, two with healthy volunteers and one each with patients suffering from perennial rhinitis and the common cold.

MATERIAL AND METHODS

The pharmacokinetics of ipratropium bromide nasal spray versus placebo were studied in two trials that used healthy volunteers as subjects. Three dosage strengths were evaluated: 0.03%, 0.06%, and 0.12%. In separate studies, the 0.03% and 0.06% dosage strengths were evaluated in patients with perennial rhinitis, and the 0.06% dosage strength was evaluated in patients with an

induced common cold. The dosage used in all four trials was two sprays per nostril, equivalent to 42 μ g (0.03%), 84 μ g (0.06%), or 168 μ g (0.12%) per nostril, depending on the protocol.

The two trials involving healthy volunteers ($n = 17$) had identical designs.⁸ A single dose of each treatment was given in a double-blind manner with placebo crossover; there was a 7-day washout period between treatments. Vital signs and pupillary diameters were assessed to determine systemic anticholinergic effects. Plasma ipratropium concentrations during a 4-hour period and the amount of ipratropium excreted in urine in a 24-hour interval were quantitated using a radioreceptor assay. The radioreceptor assay measured the active ipratropium portion of the molecule only; it quantitates by comparing the competition between ipratropium and a tritiated analogue (*N*-methylscopolamine) for binding to muscarinic receptors.⁹ The radioreceptor assay is capable of measuring concentrations from 0.1 ng/ml through 10 ng/ml by the direct addition of sample. Anything above the upper limit of 10 ng/ml was diluted into the measurable range; anything lower than 0.1 ng/ml was reported as below the limit of quantitation.

The study of perennial rhinitis involved patients who had been taking ipratropium nasal spray for at least 1 year in a long-term safety and efficacy trial of the drug ($n = 8$). Plasma and 24-hour urine samples were assessed for ipratropium after it had been administered three times a day.¹⁰

The trial that involved patients with an induced common cold ($n = 40$) used the same urine and plasma assessment methods as the studies of healthy volunteers. A parallel single-dose pharmacokinetic assessment that was done 1 day prior to the induction of the cold compared 22 patients who used ipratropium nasal spray and 18 patients who used the saline vehicle of the spray (Fig. 2). A human rhinovirus 39 was then administered to all 40 patients to induce a common cold (day 0). At the peak of nasal inflammation on day 3, a second single-dose assessment was done in an identical manner to the first-stage assessment. On day 4, patients began to take ipratropium bromide (0.06% dosage strength) nasal

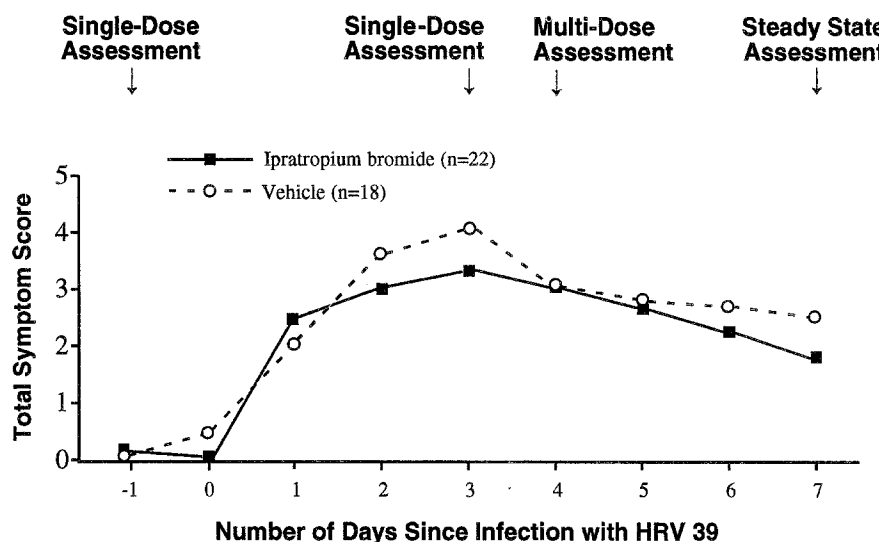


FIG. 2. Assessment protocol for pharmacokinetic comparison of ipratropium bromide nasal spray (0.06%) with its saline vehicle in healthy volunteers and in the same subjects after infection with human rhinovirus 39.

spray; 2 sprays (84 μ g/nostril) four times a day; administration continued for a total of 4 days. Amounts of ipratropium in urine were assessed on days 4 and 7, whereas plasma ipratropium concentrations were assessed on day 6 following the fourth dose of the day and on day 7 following the first dose of the day.

RESULTS

Normal volunteers

In both studies with healthy volunteers, approximately 4% to 5% of the ipratropium bromide administered was excreted unchanged into the urine, as measured at 24 hours. In a trial by Ensing et al.⁴ in which ipratropium bromide was administered intravenously, a mean of 46% of the unchanged drug was excreted in the urine. The excreted amount that was measured in our trials, therefore, would correspond to approximately 10% absorption following nasal administration. The pharmacokinetics of the drug appear to be linear, as the 4% to 5% amount excreted remained constant over the 0.03% to 0.12% dosage strength range. This is consistent with the linear pharmacokinetics observed following oral administration of up to 20 mg.⁴

Pupillary diameters were measured using 1:1 photographs taken with Polaroid film (Polaroid Corp. Medical Products, Cambridge, Mass.) capable of detecting a 0.1 mm change. There were no significant differences in mean pupillary diameter in subjects given ipratropium bromide nasal spray and placebo (Fig. 3). Vital signs were also measured. Again, there were no differences in mean diastolic and systolic

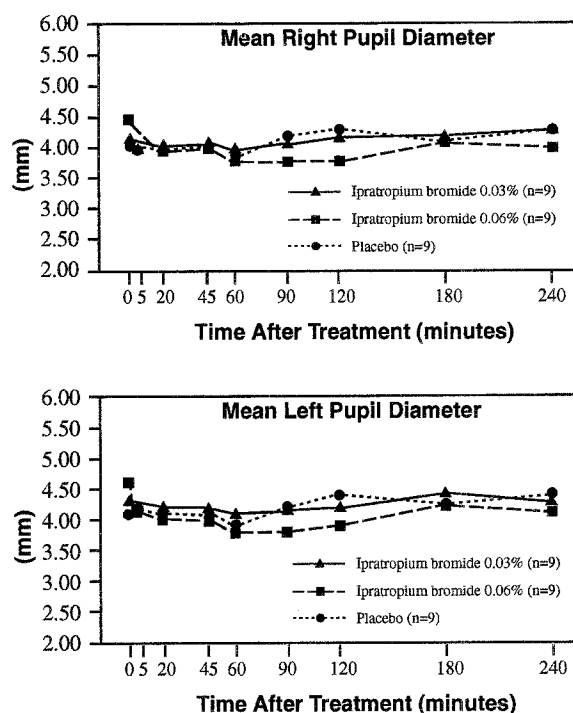


FIG. 3. Pupillary measurements after administration of ipratropium bromide (0.03% and 0.06%) and its saline vehicle in healthy volunteers.

blood pressures or pulse rates for the first 4 hours after administration of the drug or placebo. At no time during the 4 hours that we measured pupillary diameters and vital signs did plasma ipratropium concentrations become detectable in the subjects

TABLE I. Percentage of ipratropium bromide excreted into the urine unchanged during a 24-hour period following long-term intranasal administration (three times daily) in perennial rhinitis patients

Patient No.	Sex	Duration of treatment (mo)	Dosage strength	Amount excreted (μ g)	Percentage of dose
507	F	10.5	0.03%	9.672	3.8
547	M	15.0	0.03%	3.891	4.6
549	F	14.2	0.03%	6.808	8.1
560	M	13.2	0.03%	4.998	6.0
410	M	15.4	0.06%	13.705	4.1
443	F	15.4	0.06%	12.839	3.8
446	F	14.8	0.06%*	4.581	2.8
454	F	13.6	0.06%*	6.660	4.0

*One spray per nostril.

given 0.03% or 0.06% dosage strengths. With the 0.12% nasal spray, 5 of 90 samples collected during the first 4 hours demonstrated detectable concentrations; none of these exceeded 0.25 ng/ml. All concentrations were below the 1.8 ng/ml value at which intravenous ipratropium bromide has been shown to produce measurable systemic anticholinergic responses.⁴

Patients with perennial rhinitis

Ipratropium pharmacokinetics in patients with perennial rhinitis were comparable to those in healthy volunteers. Approximately 10% of the intranasal drug was absorbed in these patients, as measured by 24-hour urine excretion. There were no detectable plasma ipratropium concentrations with the 0.03% dosage strength and very few with the 0.06% dosage strength. Plasma ipratropium concentrations did not exceed 0.5 ng/ml in any of the patients, and the drug was rapidly eliminated (within 2 hours). These patients had used ipratropium bromide nasal spray three times a day for at least 1 year; there was no evidence, therefore, of long-term accumulation with chronic administration of the drug (Table I). Gender analysis demonstrated no difference in the amount excreted, and therefore in absorption, between men ($n = 3$) and women ($n = 5$).

Patients with an induced common cold

There were no significant differences in absorption pharmacokinetics between single (Table II) and multiple (Table III) dose administration of ipratropium bromide nasal spray 0.06%; nor were there any

TABLE II. Summary data of ipratropium in urine and plasma for 22 subjects on days -1 and 3*

	Day -1	Day 3
Urine		
Mean amount of ipratropium (μ g) (SE)	10.6 (1.9)	9.8 (1.8)
Mean percentage of dose (SE)	6.3% (1.2%)	5.8% (1.1%)
Plasma		
No. of subjects with detectable levels	17/22	10/22
Highest plasma level (pg/ml)	510	590

*Includes only subjects who received ipratropium bromide nasal spray.

TABLE III. Summary data of ipratropium in urine for 22 subjects on days 4 and 7 (four doses given on each day)*

	Day 4	Day 7
Urine		
Mean amount (μ g) (SE)	48.9 (8.1)	54.5 (7.6)
Mean percentage of dose (SE)	7.3% (1.2%)	8.1% (1.1%)

*Includes only subjects who received ipratropium bromide nasal spray.

significant differences in single-dose pharmacokinetics for healthy volunteers and the same patients with experimentally induced colds at the peak of inflammation. Plasma ipratropium concentrations and the percentage of drug excreted in urine in a 24-hour interval were similar to those found in the studies previously described. Fewer patients had detectable plasma ipratropium concentrations on day 3 compared with pre-cold induction; this may have been due to congestion or other infection-related factors that prevent the spray from getting to the nasal membrane (Table II). Plasma ipratropium concentrations accumulated to about 0.5 to 1.0 ng/ml by the fourth dose in the evening, but they were cleared overnight. These accumulations were observed only during a single period in which the drug was administered four times a day, and they were not chronic or clinically significant. As with patients who had perennial rhinitis, there were no absorption differences between men and women.

In this parallel group trial, no significant differences were seen in pupillary diameter measure-

TABLE IV. Compilation of percentage of unchanged ipratropium excreted by the kidneys during a 24-hour period after a single dose was administered to human subjects by various routes

Route	Dose	Mean % excreted in 24-hr urine unchanged	Reference
Intravenous	1 mg	46.0%	Adlung et al. ⁶
Intravenous	2 mg	46.0%	Ensing et al. ⁴
Inhalation	2 mg	3.10%	
Oral	2 mg	0.60%	
	5 mg	0.60%	
	10 mg	0.70%	
	20 mg	0.60%	
	500 µg	0.70%	†
Inhalation (nebu- lizer)			
Inhalation	36 µg*	11.9%	†
Intranasal	(aerosol)		
	84 µg	3.7%	This study
	168 µg	5.1%	
	168 µg	6.3%	
	336 µg	3.4%	

*Dose expressed as through the mouthpiece.

†Data on file at Boehringer Ingelheim Pharmaceuticals, Ridgefield, Conn.

ment of subjects in the ipratropium group and the placebo group with single-dose administration prior to infection, at the peak of inflammation, or on day 7 when the cold was resolving. There was only one time point at which significant differences were noted, and these were in the opposite direction (constriction) of the expected clinical response to an anticholinergic agent (Fig. 4).

CONCLUSIONS

The results of studies in three distinct populations indicate that approximately 10% of active drug is absorbed systemically after intranasal administration of ipratropium bromide. There were no significant pharmacokinetic differences between healthy volunteers and patients with either perennial rhinitis or an induced common cold. Quantifiable plasma ipratropium concentrations in the three dosage strengths tested (0.03%, 0.06%, and 0.12%) were infrequently seen; in most patients, the plasma ipratropium concentrations were below 0.1 ng/ml. Plasma ipratropium concentrations were always undetectable after the 0.03% dosage strength was used. Use of the 0.06% strength resulted in infrequent, low, transient detectable concentrations that did not appear to be

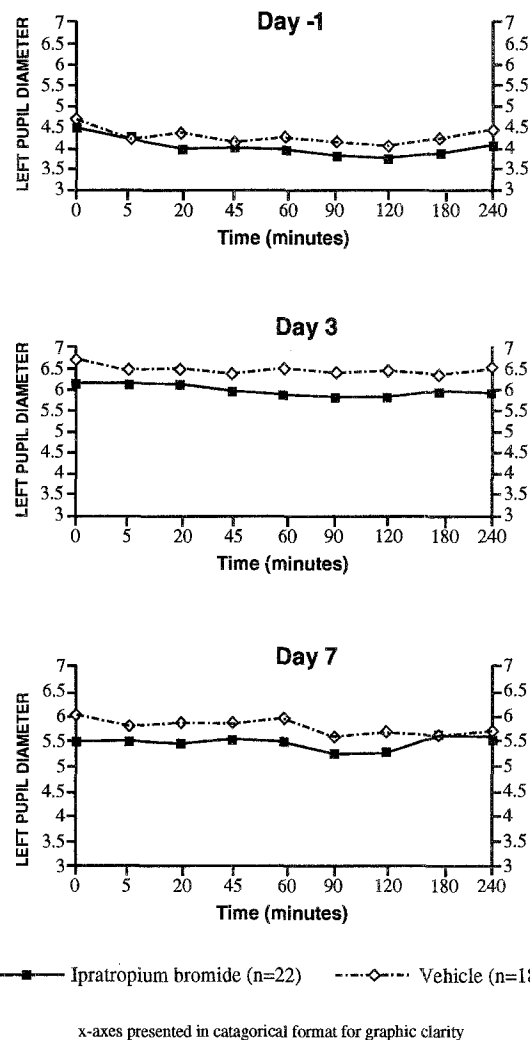


FIG. 4. Comparison of pupillary measurements after administration of ipratropium bromide (0.06%) and its saline vehicle in healthy volunteers and in the same subjects after infection with rhinovirus 39 (days 3 and 7).

of any clinical significance, as indicated by the absence of physiologic changes or adverse events consistent with systemic anticholinergic effects in these studies. These plasma ipratropium concentrations were typically seen within the first 15 minutes and were rapidly cleared 1 to 2 hours after administration.

These studies indicate that nasal administration of ipratropium bromide results in a higher extent of absorption than administration with oral or aqueous inhalation formulations (Table IV). This may be the result of depositing the drug directly in a small, highly vascular cavity where it remains stable and can continue to be absorbed over time. The absorption of 10% or less that occurred with nasal administration in these trials is quite minor,

however. It is significantly less than the percentage absorbed after aerosol administration of ipratropium bromide in the lungs, and absorption after aerosol administration has been shown to result in few if any systemic anticholinergic side effects.

From a pharmacokinetic perspective, ipratropium bromide nasal spray would seem to be truly local in its effects. It works directly on the nasal secretory glands, and any drug absorbed is rapidly eliminated. Most of the administered drug is cleared to the oropharynx and the gastrointestinal tract, where it is degraded and eliminated without absorption.

REFERENCES

1. Raphael GD, Baraniuk JN, Kaliner MH. How the nose runs and why. *J ALLERGY CLIN IMMUNOL* 1991;7:457-67.
2. Gross NJ. Ipratropium bromide. *N Engl J Med* 1988;319:486-94.
3. Eugell DW. Clinical pharmacology and toxicology of ipratropium bromide. *Am J Med* 1986;81 (suppl 5A):18-22.
4. Ensing K, de Zeeuw RA, Nossent GD, Koeter GH, Cornelissen PJG. Pharmacokinetics of ipratropium bromide after single dose inhalation and oral and intravenous administration. *Eur J Clin Pharmacol* 1989;36:189-94.
5. Bauer R, Kuhn FJ, Stockhaus K, Wick H. General pharmacology and secretion inhibitory action of (8r)-3 α -hydroxy-8-isopropyl-1 α H, 5 α H-tropiumbromide $-(\pm)$ -tropate (ipratropium bromide). *Arzneimittelforschung* 1976;26:974-80.
6. Adlung VJ, Hohle KD, Zeren S, Wahl D. Studies on pharmacokinetics and biotransformation of ipratropium bromide. *Arzneimittelforschung* 1976;26:1005-10.
7. Ensinger HA, Wahl D, Branth V. Radioreceptor assay for determination of the antimuscarinic drug ipratropium bromide in man. *Eur J Clin Pharmacol* 1987;33:459-62.
8. MacGregor TR, Wood CC, Shragis ED, Roszko PJ. Evaluation of the systemic absorption and excretion of intranasal ipratropium bromide in healthy volunteers [Abstract]. *J ALLERGY CLIN IMMUNOL* 1992;89:182.
9. Ensing K, Pol M, de Zeeuw RA. Radioreceptor assays of ipratropium bromide in plasma and urine. *J Pharm Biomed Analysis* 1988;6:433-9.
10. Grossman J, MacGregor T, Wood C, Shragis E, Roszko P. Evaluation of the systemic absorption and excretion of intra-nasal ipratropium bromide following chronic administration in perennial rhinitis patients [Abstract]. *J ALLERGY CLIN IMMUNOL* 1992;89:183.