

No Simple Markers of HPV Risk in Older Women

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VANCOUVER, B.C. — There's no easy way to identify older women whose risk for human papillomavirus infection is low, so physicians should continue cervical screening unless the woman has tested negative consistently for the virus, Concepcion Diaz-Arrastia, M.D., and her associates advised in a poster presentation at the 22nd International Papillomavirus Conference.

Nineteen (11%) of 176 women older than 55 years tested positive for infection with high-risk or intermediate-risk types of the human papillomavirus (HPV) in a prospective, longitudinal study, they reported at the conference, sponsored by the University of California, San Francisco.

"High-risk HPV infection is not restricted to young women," said Dr. Diaz-Arrastia of the University of Texas, Galveston, and her associates.

All the women completed a detailed

medical and sexual history form and underwent a pelvic exam. The study found no clear social markers of risk for HPV infection in this group of older women, whose mean age was 67 years.

More than a third of the HPV-positive women said they had been sexually inactive for more than the past 5 years. There were no significant differences between the HPV-positive and negative women in terms of the traditional social risk factors for cervical neoplasia, including a history

of first sexual activity before age 16, number of lifetime sexual partners, presence of other sexually transmitted disease, history of sexual abuse, or smoking habits.

Pap results did not correlate with risk for infection. In the HPV-positive group, two women had atypical squamous cells of undetermined significance (ASC-US), and one woman had low-grade squamous intraepithelial lesions (LSIL). In the HPV-negative group, Pap results showed ASC-US in five women and LSIL in one woman. ■



Brief Summary of Prescribing Information

INDICATIONS AND USAGE

ATROVENT HFA (ipratropium bromide HFA) Inhalation Aerosol is indicated as a bronchodilator for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema.

CONTRAINDICATIONS

ATROVENT HFA (ipratropium bromide HFA) Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to ipratropium bromide or other ATROVENT HFA Inhalation Aerosol components. ATROVENT HFA Inhalation Aerosol is also contraindicated in patients who are hypersensitive to atropine or its derivatives.

WARNINGS

ATROVENT HFA (ipratropium bromide HFA) Inhalation Aerosol is a bronchodilator for the maintenance treatment of bronchospasm associated with COPD and is not indicated for the initial treatment of acute episodes of bronchospasm where rescue therapy is required for rapid response.

Immediate hypersensitivity reactions may occur after administration of ipratropium bromide, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis and oropharyngeal edema.

Inhaled medicines, including ATROVENT HFA (ipratropium bromide HFA) Inhalation Aerosol, may cause paradoxical bronchospasm. If this occurs, treatment with ATROVENT HFA (ipratropium bromide HFA) Inhalation Aerosol should be stopped and other treatments considered.

PRECAUTIONS

General

ATROVENT HFA (ipratropium bromide HFA) Inhalation Aerosol should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy or bladder-neck obstruction.

Information for Patients

Appropriate and safe use of ATROVENT HFA Inhalation Aerosol includes providing the patient with the information listed below and an understanding of the way it should be administered (Please see complete Prescribing Information, including Patient's Instructions for Use, at http://www.bidocs.com/retent/Prescribing+Information/Pls/Atrovent+HFA/10003001_US_1.pdf?DMW_FORMAT=pdf or call 1-800-542-6257).

Patients should be advised that ATROVENT HFA (ipratropium bromide HFA) Inhalation Aerosol is a bronchodilator for the maintenance treatment of bronchospasm associated with COPD and is not indicated for the initial treatment of acute episodes of bronchospasm where rescue therapy is required for rapid response.

Patients should be cautioned to avoid spraying the aerosol into their eyes and be advised that this may result in precipitation or worsening of narrow-angle glaucoma, mydriasis, eye pain or discomfort, temporary blurring of vision, visual halos or colored images in association with red eyes from conjunctival and corneal congestion. Patients should also be advised that should any combination of these symptoms develop, they should consult their physician immediately.

The action of ATROVENT HFA Inhalation Aerosol should last 2-4 hours. Patients should be advised not to increase the dose or frequency of ATROVENT HFA Inhalation Aerosol without patients consulting their physician. Patients should also be advised to seek immediate medical attention if treatment with ATROVENT HFA Inhalation Aerosol becomes less effective for symptomatic relief, their symptoms become worse, and/or patients need to use the product more frequently than usual.

Patients should be advised on the use of ATROVENT HFA[®] Inhalation Aerosol in relation to other inhaled drugs.

Patients should be reminded that ATROVENT HFA Inhalation Aerosol should be used consistently as prescribed throughout the course of therapy.

Patients should be advised that although the taste and inhalation sensation of ATROVENT HFA Inhalation Aerosol may be slightly different from that of the CFC (chlorofluorocarbon) formulation of ATROVENT Inhalation Aerosol, they are comparable in terms of safety and efficacy.

Drug Interactions

ATROVENT HFA Inhalation Aerosol has been used concomitantly with other drugs, including sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids, that may be used in the treatment of chronic obstructive pulmonary disease. With the exception of albuterol, there are no formal studies fully evaluating the interaction effects of ATROVENT and these drugs with respect to effectiveness.

Anticholinergic agents: Although ipratropium bromide is minimally absorbed into the systemic circulation, there is some potential for an additive interaction with concomitantly used anticholinergic medications. Caution is therefore advised in the co-administration of ATROVENT HFA Inhalation Aerosol with other anticholinergic-containing drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In two-year oral carcinogenicity studies in rats and mice ipratropium bromide at oral doses up to 6 mg/kg (approximately 240 and 120 times the maximum recommended daily inhalation dose in adults on a mg/m² basis) showed no carcinogenic activity. Results of various mutagenicity studies (Ames test, mouse dominant lethal test, mouse micronucleus test and chromosome aberration of bone marrow in Chinese hamsters) were negative.

Fertility of male or female rats at oral doses up to 50 mg/kg (approximately 2000 times the maximum recommended daily inhalation dose in adults on a mg/m² basis) was unaffected by ipratropium bromide administration. At an oral dose of 500 mg/kg (approximately 20,000 times the maximum recommended daily inhalation dose in adults on a mg/m² basis), ipratropium bromide produced a decrease in the conception rate.

Pregnancy

Teratogenic Effects, Pregnancy Category B

Oral reproduction studies were performed at doses of 10 mg/kg/day in mice, 1,000 mg/kg in rats and 125 mg/kg/day in rabbits. These doses correspond, in each species, respectively, to approximately 200, 40,000 and 10,000 times the maximum recommended daily inhalation dose in adults on a mg/m² basis. Inhalation reproduction studies were conducted in rats and rabbits at doses of 1.5 and 1.8 mg/kg (approximately 60 and 140 times the maximum recommended daily inhalation dose in adults on a mg/m² basis). These studies demonstrated no evidence of teratogenic effects as a result of ipratropium bromide. At oral doses of 90 mg/kg and above in rats (approximately 3600 times the maximum recommended daily inhalation dose in adults on a mg/m² basis) embryotoxicity was observed as increased resorption. This effect is not considered relevant to human use due to the large doses at which it was observed and the difference in route of administration. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ATROVENT HFA Inhalation Aerosol should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether the active component, ipratropium bromide, is excreted in human milk. Although lipid-insoluble quaternary cations pass into breast milk, it is unlikely that ipratropium bromide would reach the infant to an important extent, especially when taken by aerosol. However, because many drugs are excreted in human milk, caution should be exercised when ATROVENT HFA Inhalation Aerosol is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

Geriatric Use

In the pivotal 12-week study, both ATROVENT HFA Inhalation Aerosol and ATROVENT Inhalation Aerosol CFC formulations were equally effective in patients over 65 years of age and under 65 years of age.

Of the total number of subjects in clinical studies of ATROVENT HFA Inhalation Aerosol, 57% were ≥65 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

ADVERSE REACTIONS

The adverse reaction information concerning ATROVENT HFA (ipratropium bromide HFA) Inhalation Aerosol is derived from two 12-week, double-blind, parallel group studies and one open-label, parallel group study that compared ATROVENT HFA Inhalation Aerosol, ATROVENT Inhalation Aerosol CFC, and placebo (in one study only) in 1,010 COPD patients. The following table lists the incidence of adverse events that occurred at a rate of greater than or equal to 3% in any ipratropium bromide group. Overall, the incidence and nature of the adverse events reported for ATROVENT HFA Inhalation Aerosol, ATROVENT Inhalation Aerosol CFC, and placebo were comparable.

TABLE 1 Adverse Experiences Reported in ≥ 3% of Patients in any Ipratropium Bromide Group

	Placebo-controlled 12 week Study 244.1405 and Active-controlled 12 week Study 244.1408			Active-controlled 1-year Study 244.2453	
	Atrovent HFA (N=243) %	Atrovent CFC (N=183) %	Placebo (N=128) %	Atrovent HFA (N=305) %	Atrovent CFC (N=151) %
Total With Any Adverse Event	63	68	72	91	87
BODY AS A WHOLE - GENERAL DISORDERS					
back pain	2	3	2	7	3
headache	6	9	8	7	5
influenza-like symptoms	4	2	2	8	5
CENTR & PERIPH NERVOUS SYSTEM DISORDERS					
dizziness	3	3	2	3	1
GASTRO-INTESTINAL SYSTEM DISORDERS					
dyspepsia	1	3	1	5	3
mouth dry	4	2	2	2	3
nausea	4	1	2	4	4
RESPIRATORY SYSTEM DISORDERS					
bronchitis	10	11	6	23	19
COPD exacerbation	8	14	13	23	23
coughing	3	4	6	5	5
dyspnea	8	8	4	7	4
rhinitis	4	2	4	6	2
sinusitis	1	4	3	11	14
upper resp tract infection	9	10	16	34	34
URINARY SYSTEM DISORDERS					
urinary tract infection	2	3	1	10	8

In the one open label controlled study in 456 COPD patients, the overall incidence of adverse events was also similar between ATROVENT HFA Inhalation Aerosol and ATROVENT Inhalation Aerosol CFC formulations. Overall, in the above mentioned studies, 9.3% of the patients taking 42 mcg ATROVENT HFA Inhalation Aerosol and 8.7% of the patients taking 42 mcg ATROVENT Inhalation Aerosol CFC reported at least one adverse event that was considered by the investigator to be related to the study drug. The most common drug-related adverse events were dry mouth (1.6% of ATROVENT HFA Inhalation Aerosol and 0.9% of ATROVENT Inhalation Aerosol CFC patients), and taste perversion (bitter taste) (0.9% of ATROVENT HFA Inhalation Aerosol and 0.3% of ATROVENT Inhalation Aerosol CFC patients).

As an anticholinergic drug, cases of precipitation or worsening of narrow-angle glaucoma, mydriasis, acute eye pain, hypotension, urinary retention, tachycardia, constipation, bronchospasm, including paradoxical bronchospasm have been reported.

Allergic-type reactions such as skin rash, angioedema of tongue, lips and face, urticaria (including giant urticaria), laryngospasm and anaphylactic reaction have been reported (see **CONTRAINDICATIONS**).

Post-Marketing Experience

Post-marketing experience with ATROVENT Inhalation Aerosol CFC in a 5-year placebo-controlled study, found that hospitalizations for supraventricular tachycardia and atrial fibrillation occurred with an incidence rate of 0.5% in patients receiving ATROVENT Inhalation Aerosol CFC.

Allergic-type reactions such as skin rash, angioedema of tongue, lips and face, urticaria (including giant urticaria), laryngospasm and anaphylactic reactions have been reported, with positive rechallenge in some cases. Many of the patients had a history of allergies to other drugs and/or foods, including soybean.

Additionally, urinary retention, mydriasis, and bronchospasm, including paradoxical bronchospasm, have been reported during the post-marketing period with use of ATROVENT Inhalation Aerosol CFC.

OVERDOSAGE

Acute overdose by inhalation is unlikely since ipratropium bromide is not well absorbed systemically after inhalation or oral administration. Oral median lethal doses of ipratropium bromide were greater than 1000 mg/kg in mice (approximately 20,000 times the maximum recommended daily inhalation dose in adults on a mg/m² basis); 1,700 mg/kg in rats (approximately 68,000 times the maximum recommended daily inhalation dose in adults on a mg/m² basis); and 400 mg/kg in dogs (approximately 53,000 times the maximum recommended daily inhalation dose in adults on a mg/m² basis).

DOSE AND ADMINISTRATION

Patients should be instructed on the proper use of their inhaler (Please see complete Prescribing Information, including Patient's Instructions for Use, at http://www.bidocs.com/retent/Prescribing+Information/Pls/Atrovent+HFA/10003001_US_1.pdf?DMW_FORMAT=pdf or call 1-800-542-6257).

Patients should be advised that although ATROVENT HFA (ipratropium bromide HFA) Inhalation Aerosol may have a slightly different taste and inhalation sensation than that of an inhaler containing ATROVENT Inhalation Aerosol, they are comparable in terms of the safety and efficacy.

ATROVENT HFA Inhalation Aerosol is a solution aerosol that does not require shaking. However, as with any other metered dose inhaler, some coordination is required between actuating the canister and inhaling the medication. Patients should "prime" or actuate ATROVENT HFA Inhalation Aerosol before using for the first time by releasing 2 test sprays into the air away from the face. In cases where the inhaler has not been used for more than 3 days, prime the inhaler again by releasing 2 test sprays into the air away from the face. Patients should avoid spraying ATROVENT HFA Inhalation Aerosol in their eyes.

The usual starting dose of ATROVENT HFA Inhalation Aerosol is two inhalations four times a day. Patients may take additional inhalations as required; however, the total number of inhalations should not exceed 12 in 24 hours. Each actuation of ATROVENT HFA Inhalation Aerosol delivers 17 mcg of ipratropium bromide from the mouthpiece.

HOW SUPPLIED

ATROVENT HFA (ipratropium bromide HFA) Inhalation Aerosol is supplied in a 12.9 g pressurized stainless steel canister as a metered-dose inhaler with a white mouthpiece that has a clear, colorless sleeve and a green protective cap (NDC 0597-0087-17).

The ATROVENT HFA Inhalation Aerosol canister is to be used only with the accompanying ATROVENT HFA Inhalation Aerosol mouthpiece. This mouthpiece should not be used with other aerosol medications. Similarly, the canister should not be used with other mouthpieces. Each actuation of ATROVENT HFA Inhalation Aerosol delivers 21 mcg of ipratropium bromide from the valve and 17 mcg from the mouthpiece. Each 12.9 gram canister provides sufficient medication for 200 actuations. The canister should be discarded after the labeled number of actuations has been used. The amount of medication in each actuation cannot be assured after this point, even though the canister is not completely empty.

Store at 25°C (77°F). Excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. For optimal results, the canister should be at room temperature before use. Patients should be reminded to read and follow the accompanying "Instructions for Use", which should be dispensed with the product.

Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw the inhaler into a fire or incinerator.

Warning: Keep out of children's reach. Avoid spraying in eyes.

Rx only

Manufactured for:
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