



BY MARY ANNE JACKSON, M.D.

ID CONSULT

Hot Topics (Other Than Influenza)

Influenza is the big 2005 infectious disease story that will continue into 2006. Here are some other important current ID topics that you may have heard less about:

► **Empyema.** Routine use of the conjugate pneumococcal vaccine does not appear to have decreased the incidence of empyema in children, although it has reduced the number of cases caused by *Streptococcus pneumoniae*. Now we're seeing increasing numbers due to methicillin-resistant *Staphylococcus aureus*.

Of 230 children (mean age 4.0 years) diagnosed in Houston between 1993 and 2002 with community-acquired pneumo-

nia and empyema, 32% of the 219 who had pleural fluid cultures performed were positive, while another 27 had a cause identified by blood culture (Pediatrics 2004;113:1735-40).

The number of children admitted for empyema per 10,000 total hospital admissions increased steadily from 5.8 in 1993-1994 to 13 in 1997-1998 to a peak of 23 in 1999-2000. The rate then dropped to 12.6/10,000 in 2001-2002, primarily due to

a drop in cases caused by *S. pneumoniae*, which accounted for 29 of 44 positive isolates (66%) in 1999-2000, compared with just 4 of 15 (27%) in 2001-2002. We may now be seeing more cases due to nonvaccine strains.

Meanwhile, isolation of *S. aureus* increased from 8 of 44 positive isolates (18%) in 1999-2000 to 9 of 15 (60%) in 2001-2002, of which the majority were in children under 1 year of age.

Half (4/8) of those seen in 1999-2000 were MRSA, versus more than three-fourths (7/9) in 2001-2002.

The authors concluded—and I agree—that if you live in a community in which MRSA now accounts for more than 10% of invasive infections, vancomycin plus ceftriaxone should be the first-line empiric therapy for empyema and pleural effusions associated with community-acquired

Xopenex HFA™

(levalbuterol tartrate) Inhalation Aerosol

FOR ORAL INHALATION ONLY

BRIEF SUMMARY

INDICATIONS AND USAGE

XOPENEX HFA (levalbuterol tartrate) Inhalation Aerosol is indicated for the treatment or prevention of bronchospasm in adults, adolescents, and children 4 years of age and older with reversible obstructive airway disease.

CONTRAINDICATIONS

XOPENEX HFA (levalbuterol tartrate) Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to levalbuterol, racemic albuterol, or any other component of XOPENEX HFA Inhalation Aerosol.

WARNINGS

1. **Paradoxical Bronchospasm:** Like other inhaled beta-adrenergic agonists, XOPENEX HFA Inhalation Aerosol can produce paradoxical bronchospasm, which may be life-threatening. If paradoxical bronchospasm occurs, XOPENEX HFA (levalbuterol tartrate) Inhalation Aerosol should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister. 2. **Deterioration of Asthma:** Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of XOPENEX HFA Inhalation Aerosol than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

3. **Use of Anti-inflammatory Agents:** The use of a beta-adrenergic agonist alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids, to the therapeutic regimen. 4. **Cardiovascular**

Effects: XOPENEX HFA Inhalation Aerosol, like other beta-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients, as measured by heart rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of XOPENEX HFA Inhalation Aerosol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, XOPENEX HFA Inhalation Aerosol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. 5. **Do Not Exceed Recommended Dose:** Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected. 6. **Immediate Hypersensitivity Reactions:** Immediate hypersensitivity reactions may occur after administration of racemic albuterol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema. The potential for hypersensitivity must be considered in the clinical evaluation of patients who experience immediate hypersensitivity reactions while receiving XOPENEX HFA Inhalation Aerosol.

PRECAUTIONS

General

XOPENEX HFA (levalbuterol tartrate) Inhalation Aerosol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, hypertension, and cardiac arrhythmias; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after the use of any beta-adrenergic bronchodilator.

Large doses of intravenous racemic albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. As with other beta-adrenergic agonist medications, XOPENEX HFA Inhalation Aerosol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Information for Patients

The action of XOPENEX HFA Inhalation Aerosol should last for 4 to 6 hours. XOPENEX HFA Inhalation Aerosol should not be used more frequently than recommended. Do not increase the dose or frequency of doses of XOPENEX HFA Inhalation Aerosol without consulting your physician. If you find that treatment with XOPENEX HFA Inhalation Aerosol becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, you should seek medical attention immediately. While you are using XOPENEX HFA Inhalation Aerosol, other inhaled drugs and asthma medications should be taken only as directed by your physician. Common adverse effects of treatment with inhaled beta-agonists include palpitations, chest pain, rapid heart rate, tremor, and nervousness. If you are pregnant or nursing, contact your physician about use of XOPENEX HFA Inhalation Aerosol. Effective and safe use of XOPENEX HFA Inhalation Aerosol includes an understanding of the way that it should be administered.

Use XOPENEX HFA Inhalation Aerosol only with the actuator supplied with the product. Discard the canister after 200 sprays have been used. Never immerse the canister in water to determine how full the canister is ("float test").

In general, the technique for administering XOPENEX HFA Inhalation Aerosol to children is similar to that for adults. Children should use XOPENEX HFA Inhalation Aerosol under adult supervision, as instructed by the patient's physician.

Drug Interactions

Other short-acting sympathomimetic aerosol bronchodilators or epinephrine should be used with caution with XOPENEX HFA Inhalation Aerosol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

1. **Beta-blockers:** Beta-adrenergic receptor-blocking agents not only block the pulmonary effect of beta-adrenergic agonists, such as XOPENEX HFA Inhalation Aerosol, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers should be considered, although they should be administered with caution. 2. **Diuretics:** The ECG changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop and thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non-potassium-sparing diuretics. 3. **Digoxin:** Mean decreases of 16% to 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of racemic albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving XOPENEX HFA Inhalation Aerosol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and XOPENEX HFA Inhalation Aerosol. 4. **Monoamine Oxidase Inhibitors or Tricyclic Antidepressants:** XOPENEX HFA Inhalation Aerosol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the vascular system may be potentiated.

Carcinogenesis, Mutagenesis, and Impairment of Fertility No carcinogenesis or impairment of fertility studies have been carried out with levalbuterol tartrate. However, racemic albuterol sulfate has been evaluated for its carcinogenic potential and ability to impair fertility.

In a 2-year study in Sprague-Dawley rats, racemic albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at, and above, dietary doses of 2 mg/kg/day (approximately 30 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m² basis and approximately 15 times the maximum recommended daily inhalation dose of levalbuterol tartrate for children on a mg/m² basis). In another study, this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist. In an 18-month study in CD-1 mice, racemic albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 500 mg/kg/day (approximately 3800 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m² basis and approximately 1800 times the maximum recommended daily inhalation dose of levalbuterol tartrate for children on a mg/m² basis). In a 22-month study in the Golden hamster, racemic albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 50 mg/kg/day (approximately 500 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m² basis and approximately 240 times the maximum recommended daily inhalation dose of levalbuterol tartrate for children on a mg/m² basis).

Levalbuterol HCl was not mutagenic in the Ames test or the CHO/HPRT Mammalian Forward Gene Mutation Assay.

Levalbuterol HCl was not clastogenic in the in vivo micronucleus test in mouse bone marrow. Racemic albuterol sulfate was negative in an in vitro chromosomal aberration assay in CHO Cell cultures.

Reproduction studies in rats using racemic albuterol sulfate demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg/day (approximately 750 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m² basis).

Teratogenic Effects - Pregnancy Category C A reproduction study in New Zealand White rabbits demonstrated that levalbuterol HCl was not teratogenic when administered orally at doses up to 25 mg/kg/day (approximately 750 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m² basis).

However, racemic albuterol sulfate has been shown to be teratogenic in mice and rabbits. A study in CD-1 mice given racemic albuterol sulfate subcutaneously showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg/day (approximately 2 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m² basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg/day (approximately 20 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m² basis). The drug did not induce cleft palate formation when administered subcutaneously at a dose of 0.025 mg/kg/day (less than the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m² basis). Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with 2.5 mg/kg/day of isoproterenol (positive control).

A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when racemic albuterol sulfate was administered orally at a dose of 50 mg/kg/day (approximately 1500 times the maximum recommended daily inhalation dose of levalbuterol tartrate for adults on a mg/m² basis).

A study in which pregnant rats were dosed with radiolabeled racemic albuterol sulfate demonstrated that drug-related material is transferred from the maternal circulation to the fetus.

There are no adequate and well-controlled studies of XOPENEX HFA Inhalation Aerosol in pregnant women. Because animal reproduction studies are not always predictive of human response, XOPENEX HFA Inhalation Aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

During marketing experience of racemic albuterol, various congenital anomalies, including cleft palate and limb defects, have been rarely reported in the offspring of patients being treated with racemic

albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between racemic albuterol use and congenital anomalies has not been established.

Use in Labor and Delivery Because of the potential for beta-adrenergic agonists to interfere with uterine contractility, the use of XOPENEX HFA Inhalation Aerosol for the treatment of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

Tocolysis XOPENEX HFA Inhalation Aerosol has not been approved for the management of preterm labor. The benefit:risk ratio when levalbuterol tartrate is administered for tocolysis has not been established. Serious adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with beta2-agonists, including racemic albuterol.

Nursing Mothers Plasma concentrations of levalbuterol after inhalation of therapeutic doses are very low in humans. It is not known whether levalbuterol is excreted in human milk.

Because of the potential for tumorigenicity shown for racemic albuterol in animal studies and the lack of experience with the use of XOPENEX HFA Inhalation Aerosol by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when XOPENEX HFA Inhalation Aerosol is administered to a nursing woman.

Pediatrics The safety and efficacy of XOPENEX HFA Inhalation Aerosol have been established in pediatric patients 4 years of age and older in an adequate and well-controlled clinical trial. Use of XOPENEX HFA Inhalation Aerosol in children is also supported by evidence from adequate and well-controlled studies of XOPENEX HFA Inhalation Aerosol in adults, considering that the pathophysiology, systemic exposure of the drug, and clinical profile in pediatric and adult patients are substantially similar. Safety and effectiveness of XOPENEX HFA Inhalation Aerosol in pediatric patients below the age of 4 years have not been established.

Geriatrics Clinical studies of XOPENEX HFA Inhalation Aerosol did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant diseases or other drug therapy.

Albuterol is known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS Adverse event information concerning XOPENEX HFA (levalbuterol tartrate) Inhalation Aerosol in adults and adolescents is derived from two 8-week, multicenter, randomized, double-blind, active- and placebo-controlled trials in 748 adult and adolescent patients with asthma that compared XOPENEX HFA Inhalation Aerosol, a marketed albuterol HFA inhaler, and an HFA-134a placebo inhaler. The following lists the incidence (% XOPENEX HFA 90 mcg, marketed albuterol HFA inhaler 180 mcg, placebo, respectively) of all adverse events (whether considered by the investigator to be related or unrelated to drug) from these trials that occurred at a rate of 2% or greater in the group treated with XOPENEX HFA Inhalation Aerosol and more frequently than in the HFA-134a placebo inhaler group. **Body as a whole:** pain (4.0%, 3.4%, 3.6%), **Central nervous system:** dizziness (2.7%, 0.6%, 1.8%), **Respiratory system:** asthma (9.4%, 7.3%, 6.0%), pharyngitis (7.9%, 2.2%, 2.4%), rhinitis (7.4%, 2.2%, 3.0%).

Adverse events reported by less than 2% and at least 2 or more of the adolescent and adult patients receiving XOPENEX HFA Inhalation Aerosol and by a greater proportion than receiving HFA-134a placebo inhaler include cyst, flu syndrome, viral infection, constipation, gastroenteritis, myalgia, hypertension, epistaxis, lung disorder, acne, herpes simplex, conjunctivitis, ear pain, dysmenorrhea, hematuria, and vaginal moniliasis. There were no significant laboratory abnormalities observed in these studies.

Adverse event information concerning XOPENEX HFA Inhalation Aerosol in children is derived from a 4-week, randomized, double-blind trial of XOPENEX HFA Inhalation Aerosol, a marketed albuterol HFA inhaler, and an HFA-134a placebo inhaler in 150 children aged 4 to 11 years with asthma. The following lists the adverse events (% XOPENEX HFA 90 mcg, marketed albuterol HFA inhaler 180 mcg, placebo, respectively) reported for XOPENEX HFA Inhalation Aerosol in children at a rate of 2% or greater and more frequently than for placebo. **Body as a whole:** accidental injury (9.2%, 10.3%, 5.7%), **Digestive system:** vomiting (10.5%, 7.7%, 5.7%), **Respiratory system:** bronchitis (2.6%, 0%, 0%), pharyngitis (6.6%, 12.8%, 5.7%).

The incidence of systemic beta-adrenergic adverse effects (e.g., tremor, nervousness) was low and comparable across all treatment groups, including placebo.

Postmarketing In addition to the adverse events reported in clinical trials, the following adverse events have been observed in postapproval use of levalbuterol inhalation solution. These events have been chosen for inclusion due to their seriousness, their frequency of reporting, or their likely beta-mediated mechanism: angioedema, anaphylaxis, arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles), asthma, chest pain, cough increased, dyspnea, nausea, nervousness, rash, tachycardia, tremor, urticaria. Because these events have been reported spontaneously from a population of unknown size, estimates of frequency cannot be made.

In addition, XOPENEX HFA Inhalation Aerosol, like other sympathomimetic agents, can cause adverse reactions such as hypertension, angina, vertigo, central nervous system stimulation, sleeplessness, headache, and drying or irritation of the oropharynx.

Rx only.

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All-Time Low in Measles Cases Reported in 2004

Measles cases in the United States have hit an all-time low, the Centers for Disease Control and Prevention reported.

During 2004, just 37 cases of measles were reported to the CDC. This number—the lowest ever reported in 1 year in the United States—represents a 16% drop from the 44 cases reported in 2002, the CDC said (MMWR 2005;54:1229-31).

Nearly half (18) of the 37 cases were children aged 1-4 years, another 7 were aged 5-19 years, 5 were younger than 12 months of age, 5 were 20-34 years old, and 2 were aged 35 years or older.

Three states—Washington, California, and New York—accounted for 49% of the cases, whereas 11 states reported one to three cases each.

Of the 37 cases, 27 (73%) were imported, including 14 in U.S. residents who had acquired measles while traveling abroad, and 13 in foreign nationals who acquired the disease abroad and subsequently traveled to the United States. China was the most frequent country from which measles was imported, accounting for 13 of the cases.

All 14 of the U.S. residents with imported measles cases were vaccine eligible. Of those, nine were not vaccinated, three had unknown vaccination status, and two had received at least one dose of measles vaccine.

Of the 13 non-U.S. residents with imported measles, 10 had not been vaccinated and 3 had unknown vaccination status.

Ten of the cases were indigenous (infectious in the United States), of which six were linked to imported cases and four had unknown sources of exposure.

It will be necessary to maintain greater than 90% vaccination coverage in the United States as long as measles is endemic in most countries worldwide, the CDC said.

—Miriam E. Tucker

pneumonia. The use of clindamycin plus ceftriaxone may be acceptable in institutions where MRSA remains susceptible to clindamycin.

Of the 212 patients for whom information on therapeutic intervention was available, 59% underwent video-assisted thoracoscopy (VATS), which is now emerging as the most cost-effective treatment for complicated pleural empyemas at the institutions where physicians have become expert at performing it.

Among the 125 children who underwent VATS, length of hospital stay was significantly shorter (12 vs. 15 days) for the 49 who underwent the procedure within 48 hours of admission, compared with the 76 children in whom VATS was performed beyond 2 days. Length of fever after hospitalization was also significantly shorter in the group who underwent early VATS (7 vs. 9 days).

► **Oral rehydration therapy.** As we anxiously await the availability of new rotavirus vaccines, we will continue to see large numbers of children with dehydration due to viral gastroenteritis during the colder months.

Intravenous fluid therapy (IVF) still is widely used even in children whose dehydration is not severe, despite evidence that oral rehydration therapy (ORT) can be initiated more quickly, is just as effective, and is well-received by patients and their families.

Among data supporting ORT are those from a study in which 73 children aged 8 weeks to 3 years who presented to an urban pediatric emergency department with mild to moderate (5%-10%) dehydration were randomized to receive either IVF or ORT (*Pediatrics* 2005;115:295-301).

There was no difference between the two groups in the overall proportion achieving successful rehydration at 4 hours (56% ORT vs. 57% IVF), urine output was similar, and no patient in either group had severe emesis.

However, more patients who received IVF had weight gain by the end of the 4 hours (100% IVF vs. 83% ORT). The mean time to initiate therapy was substantially shorter with ORT (19.9 vs. 41.2 minutes), and fewer ORT patients were hospitalized (30% vs. 49%).

Five of the 36 children randomized to ORT were unable to tolerate it and required IV placement. When analyzed by treatment received, overall successful rehydration still did not differ significantly (61% ORT vs. 62% IVF), while hospitalization was required in 23% with ORT versus 50% with IVF.

Of course, ORT isn't for everyone, including patients with hypotension, chronic underlying illness, growth failure, or oral-motor impairments. I also would advise IVF for infants less than 2 months of age and for patients who are severely dehydrated or have been sick for more than 5 days.

The addition in future of a rotavirus vaccine to our child immunization schedule may effectively reduce the need for such hydration therapy in the pediatric population.

► **Varicella.** Rates have declined so dramatically in the decade since the vaccine became available that we may be in danger of forgetting about varicella altogether. Many adolescents remain at high risk

because they were born too late to receive the vaccine as part of routine infant immunization, but they are now less likely to have been exposed to the natural virus earlier in childhood.

Of the four current routine adolescent vaccinations, varicella was the one recommended the least often by 210 pediatricians and family physicians who responded to a mailed survey (59% response rate).

Overall, 98% of respondents reported routinely recommending vaccination against tetanus-diphtheria, 90% against hepatitis B, and 84% against measles, mumps, and rubella, compared with just 60% who

reported routinely recommending varicella vaccination of susceptible adolescents (*J. Am. Board Fam. Pract.* 2005;18:13-9).

Only 68% of the respondents reported that it was "very important" to ensure that adolescents were up to date on protection against varicella, whereas 86%-97% reported the same regarding hepatitis B; measles, mumps, rubella; and tetanus-diphtheria.

Among the reasons cited by the authors is the perception that varicella is a benign illness.

In fact, in a high-risk host, the disease can result in severe secondary bacterial infection including necrotizing fasciitis and

viral dissemination to the lungs, liver, and central nervous system.

With varicella zoster immune globulin currently in short supply—and possibly for the foreseeable future—intravenous immune globulin is now the primary means of postexposure prophylaxis for susceptible individuals.

We mustn't let down our guard with varicella. It still results in pediatric deaths each year. ■

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