Multiple Pathogens Often Found in Bronchiolitis

BY DOUG BRUNK
San Diego Bureau

SAN DIEGO — Respiratory syncytial virus was the most common virus detected in young children with bronchiolitis, but nearly 40% were infected with other viruses, results from a single-center study showed.

"The results suggest that further study is warranted to learn more about the potential impact of viral pathogens associated with bronchiolitis," Hilary Stempel said at the annual meeting of the Infectious Diseases Society of America.

Ms. Stempel, a clinical research associate in infectious diseases with Children's Hospital and Regional Medical Center, Seattle, said that she and her associates undertook the study because guidelines from the American Academy of Pediatrics recommend that the diagnosis of bronchiolitis should be made on the basis of history and physical, and that clinicians should not routinely order laboratory tests for the diagnosis (Pediatrics 2006;118:1774-93).

The rationale for this position, according to the guidelines, is that "the knowledge gained from such testing rarely alters management decisions or outcomes for the vast majority of children with clinically diagnosed bronchiolitis."

However, the guidelines do state that "virologic testing may be useful when cohorting of patients is feasible."

That particular statement interested the researchers at the hospital, where "patient cohorting is still a necessity," Ms. Stempel said. "So we decided to explore the implications of viral testing for children with bronchiolitis."

Researchers collected residual nasal wash specimens from 189 children aged 0-3 years who were evaluated for bronchiolitis from October 2003 through April 2004. All specimens were evaluated with quantitative real time polymerase chain reaction testing and fluorescent antibody assay.

The median age of the 189 children was 7 months, 54% were male, and 26% had an underlying disease such as asthma or a cardiac condition.

Most samples (72%) were acquired from the general pediatric ward, while 21% were acquired from the emergency department, and 7% from the intensive care unit.

Ms. Stempel reported that a total of 220 respiratory viral pathogens were detected in 177 of the 189 children (94%). The majority of the 220 viruses were RSV (145), followed by adenovirus (28), human metapneumovirus (hMPV) (20), coronavirus (14), parainfluenza (12) and influenza (1).

'We decided to explore the implications of viral testing for children with bronchiolitis.'

MS. STEMPEL

Forty-three samples contained two or more viruses. Of these, 35 (81%) involved RSV. Other coinfections included hMPV and parainfluenza (4 samples), hMPV and adenovirus (3 samples) and parainfluenza and adenovirus (1 sample).

Limitations of the study include its retrospective design and the fact that rhinovirus assay was not performed. Also, "the study ended in April 2004 and did not extend through the entire parainfluenza season," Ms. Stempel said. "This may have lowered the number of parainfluenza infections that we detected."

Ms. Stempel disclosed that one of the study coauthors, Dr. Janet A. Englund, has received research support and consulting fees from MedImmune and Sanofi Pasteur. ■

VERBATIM

"You should be recording names of family members in every chart—for the 'family history' section, you can't put 'See siblings' charts.' What if all three children's charts have that recording?"

Dr. Charles A. Scott, p. 54

MAXAIR® AUTOHALER®
(pirbuterol acetate inhalation aerosol)
For Oral Inhalation Only
Brief Summary of Prescribing Information
See Package Insert for Full Prescribing Information

INDICATIONS AND USAGE MAXAIR AUTOHALER is indicated for the prevention and reversal of bronchospasm in patients 12 years of age and older with reversible bronchospasm including asthma. It may be used with or without concurrent theophylline and/or corticosteroid therapy. **CONTRAINDICATIONS** MAXAIR AUTOHALER is contraindicated in patients with a history of hypersensitivity to pirbuterol or any of its ingredients. **WARNINGS Cardiovascular:** MAXAIR AUTOHALER, like other inhaled beta adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure and/or symptoms. Although such effects are uncommon after administration of MAXAIR AUTOHALER at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce 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, MAXAIR AUTOHALER, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. **Paradoxical Bronchospasm:** MAXAIR AUTOHALER can produce paradoxical bronchospasm, which can be life threatening. If paradoxical bronchospasm occurs, MAXAIR AUTOHALER 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 or vial. **Use of Anti-Inflammatory Agents:** The use of beta adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids. **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 MAXAIR AUTOHALER than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and the treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids. **PRECAUTIONS General:** Since pirbuterol is a sympathomimetic amine, it should be used with caution in patients with cardiovascular disorders, including ischemic heart disease, hypertension, or cardiac arrhythmias, in patients with hyperthyroidism or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines or who have convulsive disorders. Significant changes in systolic and diastolic blood pressure could be expected to occur in some patients after use of any beta adrenergic aerosol bronchodilator. Beta adrenergic agonist medications 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 MAXAIR AUTOHALER should last up to five hours or longer. MAXAIR AUTOHALER should not be used more frequently than recommended. Do not increase the dose or frequency of MAXAIR AUTOHALER without consulting your physician. If you find that treatment with MAXAIR AUTOHALER becomes less effective for symptomatic relief, or 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 MAXAIR AUTOHALER, other inhaled drugs and asthma medications should be taken only as directed by your physician. Common adverse effects include palpitations, chest pain, rapid heart rate, tremor or nervousness. If you are pregnant or nursing, contact your physician about use of MAXAIR AUTOHALER. Effective and safe use includes an understanding of the way the medication should be administered. As with all aerosol medications, it is recommended to prime (test) MAXAIR AUTOHALER before using for the first time. MAXAIR AUTOHALER should also be primed if it has not been used in 48 hours. As described in the priming procedure, use the test fire slide to release two priming sprays into the air away from yourself and other people. (See "Patient's Instructions For Use" portion of this package insert.) The MAXAIR AUTOHALER actuator should not be used with any other inhalation aerosol canister. In addition, canisters for use with MAXAIR AUTOHALER should not be utilized with any other actuator. **Drug Interactions:** Other short-acting beta adrenergic aerosol bronchodilators should not be used concomitantly with MAXAIR AUTOHALER because they may have additive effects. **Monoamine Oxidase Inhibitors or Tricyclic Antidepressants:** Pirbuterol 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 pirbuterol on the vascular system may be potentiated. **Beta Blockers:** Beta adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as MAXAIR AUTOHALER, 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 could be considered, although they should be administered with caution. **Diuretics:** The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or 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. **Carcinogenesis, Mutagenesis and Impairment of Fertility:** In a 2-year study in Sprague-Dawley rats, pirbuterol hydrochloride administered at dietary doses of 1.0, 3.0, and 10 mg/kg (approximately 3, 10, and 35 times the maximum recommended daily inhalation dose for adults and children on a mg/m² basis) showed no evidence of carcinogenicity. In an 18-month study in mice at dietary doses of 1.0, 3.0, and 10 mg/kg (approximately 2, 5, and 15 times the maximum recommended daily inhalation dose for adults and children on a mg/m² basis) no evidence of tumorigenicity was seen. Reproduction studies in rats administered pirbuterol hydrochloride at oral doses of 1, 3, and 10 mg/kg (approximately 3, 10, and 35 times the maximum recommended daily inhalation dose for adults on a mg/m² basis) revealed no evidence of impaired fertility. Pirbuterol dihydrochloride showed no evidence of mutagenicity in *in vitro* assays and host-mediated microbial (Ames) assays for point mutations and *in vivo* tests for somatic or germ cell effects following acute and subchronic treatment in mice (cytogenicity assays). **Teratogenic Effects – Pregnancy Category C:** Pirbuterol was not teratogenic in rats administered oral doses of 30, 100, and 300 mg/kg (approximately 100, 340, and 1000 times the maximum recommended daily inhalation dose for adults on a mg/m² basis). Pirbuterol was not teratogenic in rabbits administered oral doses of 30 and 100 mg/kg (approximately 200 and 680 times the maximum recommended inhalation dose for adults on a mg/m² basis). However, pirbuterol at an oral dose of 300 mg/kg (approximately 2000 times the maximum recommended daily inhalation dose in adults on a mg/m² basis) caused abortions and fetal death. There are no adequate and well-controlled studies in pregnant women. Pirbuterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** Because of the potential for beta-agonist interference with uterine contractility, use of MAXAIR AUTOHALER for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk. **Nursing Mothers:** It is not known whether pirbuterol is excreted in human milk. Therefore, MAXAIR AUTOHALER should be used during nursing only if the potential benefit justifies the possible risk to the newborn. **Pediatric Use:** MAXAIR AUTOHALER is not recommended for patients under the age of 12 years because of insufficient clinical data to establish safety and effectiveness. **ADVERSE REACTIONS** The following rates of adverse reactions to pirbuterol are based on single- and multiple-dose clinical trials involving 761 patients, 400 of whom received multiple doses (mean duration of treatment was 2.5 months and maximum was 19 months). The following were the adverse reactions reported more frequently than 1 in 100 patients: **CNS:** nervousness (6.9%), tremor (6.0%), headache (2.0%), dizziness (1.2%). **Cardiovascular:** palpitations (1.7%), tachycardia (1.2%). **Respiratory:** cough (1.2%). **Gastrointestinal:** nausea (1.7%). The following adverse reactions occurred less frequently than 1 in 100 patients and there may be a causal relationship with pirbuterol: **CNS:** depression, anxiety, confusion, insomnia, weakness, hyperkinesia, syncope. **Cardiovascular:** hypotension, skipped beats, chest pain. **Gastrointestinal:** dry mouth, glossitis, abdominal pain/cramps, anorexia, diarrhea, stomatitis, nausea and vomiting. **Ear, Nose and Throat:** smell/taste changes, sore throat. **Dermatological:** rash, pruritus. **Other:** numbness in extremities, alopecia, bruising, fatigue, edema, weight gain, flushing. Other adverse reactions were reported with a frequency of less than 1 in 100 patients but a causal relationship between pirbuterol and the reaction could not be determined: migraine, productive cough, wheezing, and dermatitis.

The following rates of adverse reactions during three-month controlled clinical trials involving 310 patients are noted. The table does not include mild reactions.

PERCENT OF PATIENTS WITH MODERATE TO SEVERE ADVERSE REACTIONS

Reaction	Pirbuterol N=157	Metaproterenol N=153
Central Nervous System		
tremors	1.3%	3.3%
nervousness	4.5%	2.6%
headache	1.3%	2.0%
weakness	.0%	1.3%
drowsiness	.0%	0.7%
dizziness	0.6%	.0%
Cardiovascular		
palpitations	1.3%	1.3%
tachycardia	1.3%	2.0%
Respiratory		
chest pain/tightness	1.3%	.0%
cough	.0%	0.7%
Gastrointestinal		
nausea	1.3%	2.0%
diarrhea	1.3%	0.7%
dry mouth	1.3%	1.3%
vomiting	.0%	0.7%
Dermatological		
skin reaction	.0%	0.7%
rash	.0%	1.3%
Other		
bruising	0.6%	.0%
smell/taste change	0.6%	.0%
backache	.0%	0.7%
fatigue	.0%	0.7%
hoarseness	.0%	0.7%
nasal congestion	.0%	0.7%

Electrocardiograms: Electrocardiograms, obtained during a randomized, double-blind, cross-over study in 57 patients, showed no observations or findings considered clinically significant, or related to drug administration. Most electrocardiographic observations, obtained during a randomized, double-blind, cross-over study in 40 patients, were judged not clinically significant or related to drug administration. One patient was noted to have some changes on the one hour postdose electrocardiogram consisting of ST and T wave abnormality suggesting possible inferior ischemia. This abnormality was not observed on the predose or the six hours postdose ECG. A treadmill was subsequently performed and all the findings were normal. **OVERDOSAGE** The expected symptoms with overdosage are those of excessive beta-stimulation and/or any of the symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Hypokalemia may also occur. As with all sympathomimetic aerosol medication, cardiac arrest and even death may be associated with abuse of MAXAIR AUTOHALER. Treatment consists of discontinuation of pirbuterol together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage. The oral median lethal dose of pirbuterol dihydrochloride in mice and rats is greater than 2000 mg/kg (approximately 3400 and 6800 times the maximum recommended daily inhalation dose for adults on a mg/m² basis).

Note: The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFC's).

> **WARNING:** Contains trichloromonofluoromethane and dichlorodifluoromethane, substances which harm public health and environment by destroying ozone in the upper atmosphere.

A notice similar to the above WARNING has been placed in the "Patient's Instructions For Use" portion of this package insert under the Environmental Protection Agency's (EPA's) regulations. The patient's warning states that the patient should consult his or her physician if there are questions about alternatives.

This is only a brief summary of important information regarding MAXAIR AUTOHALER. For more information please visit www.maxairautohaler.com or call 1-800-328-0255.

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654800

US19 Rev0407-1

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