

GERD Tx Aids Lung Function in Asthmatic Kids

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SEATTLE — Treating gastroesophageal reflux disease in children with persistent asthma improves lung function in the long term, new data show. Moreover, medical and surgical treatments appear to work equally well.

About two-thirds of nonatopic children with persistent asthma also have gastroesophageal reflux disease (GERD), and that disease appears to exacerbate the asthma, Dr. Aaron K. Kobernick said at the annual meeting of the American College of Allergy, Asthma, and Immunology. Studies of GERD treatment in this context have focused on asthma medication use and have been relatively short.

“With asthma, short-term studies are not as reliable,” said Dr. Kobernick. “Because [it] is a disease of exacerbation and remission, the longer we look at asthma and [its] outcomes, the better.”



Large airways are exposed to the reflux acid, and they tend to respond more quickly with anti-GERD treatment.

DR. KOBERNICK

In a prospective 2-year study, Dr. Kobernick and his colleagues enrolled 62 children aged between 6 and 11 years and who had moderate persistent asthma but did not have atopy or risk factors for wheezing. At baseline, all of the children underwent spirometry and extended esophageal pH monitoring. The latter testing revealed that most also had GERD.

Of those with asthma and GERD, 32 were treated with medical therapy for GERD consisting of proton pump inhibitors and prokinetic agents and 12 underwent surgical fundoplication; they also received asthma therapy. The 18 children who did not have comorbid GERD received asthma therapy only.

The three groups were similar with respect to age, sex, socioeconomic status, duration of illness, and initial spirometry findings, noted Dr. Kobernick, a medicine and pediatrics resident at Tulane University in New Orleans.

After 2 years of treatment, the average annual number of asthma exacerbations per child was significantly lower, by about 75%, in those with medically treated GERD (0.68) and those with surgically treated GERD (0.79), compared with their GERD-free counterparts treated for asthma alone (2.9). The difference between the medically and surgically treated GERD groups was not significant.

The percentage of children who had an improvement in forced expiratory volume in 1 second (FEV₁) by more than 20% from baseline was significantly greater in the groups given medical GERD treatment (47%) and surgical GERD treatment (58%), compared with the group given asthma therapy alone (28%).

The percentage of children with an improvement in forced expiratory flow in mid-expiration (FEF_{25%-75%}) of more than 20% from baseline was significantly greater with added medical GERD therapy (22%) and surgical GERD therapy (25%), versus asthma therapy alone (11%).

Dr. Kobernick said anatomy may explain why more children had an improvement in FEV₁ (indicating large-airway function) than they did in FEF_{25%-75%}

(indicating small-airway function) with anti-GERD treatment. “Maybe the large airways... are most likely exposed to the onslaught of acid from the reflux, and those just tend to improve more quickly with anti-GERD treatment,” he said.

Spirometry testing done after only 1 year of treatment did not show any significant improvement in FEV₁, he noted. That, combined with the apparent slower improvement of FEF_{25%-75%}, reinforces

the importance of long-term studies.

The results may underestimate the benefit of anti-GERD treatment because many children had been previously treated for asthma. “The average time a patient was treated for asthma before enrollment was about 1½-2 years, so we think their lungs probably started looking a lot better before they enrolled,” said Dr. Kobernick, who reported no conflicts of interest related to the study. ■

IMPORTANT CORRECTION OF DRUG INFORMATION ABOUT BYSTOLIC® (NEBIVOLOL) TABLETS

An advertisement in professional journal publications for Bystolic® (nebivolol) tablets for the treatment of hypertension was the subject of a Warning Letter issued by the U.S. Food and Drug Administration (FDA) in August 2008.

Forest would like to take this opportunity to clarify the content of this advertisement.

Indications and Usage

Bystolic is indicated for the treatment of hypertension. Bystolic may be used alone or in combination with other antihypertensive agents.

Unsubstantiated Superiority and Mechanism of Action Claims

The FDA objected to claims that Bystolic was a novel and next generation beta blocker with a unique mechanism of action including cardioselective beta blockade and vasodilation. The FDA stated that these claims were misleading because they suggested that Bystolic is different from and superior to other β -adrenergic receptor blocking agents in the treatment of hypertension, when these implications have not been demonstrated by substantial evidence or substantial clinical experience. In extensive metabolizers (most of the population) and at doses ≤ 10 mg, Bystolic is preferentially β_1 selective. The FDA also stated that the presentation of the mechanism of action implied that it had been established, when the package insert states that the mechanism of action of the antihypertensive response of Bystolic has not been definitively established.

Omission and Minimization of Risk Information

The FDA stated that the advertisement did not disclose the following important safety information, which is contained in Bystolic's full Prescribing Information:

Warning: In patients who have compensated congestive heart failure, Bystolic should be administered cautiously. If heart failure worsens, discontinuation of Bystolic should be considered.

Precautions: CYP2D6 Inhibitors: Use caution when Bystolic is co-administered with CYP2D6 inhibitors (quinidine, propafenone, fluoxetine, paroxetine, etc).

Drug interactions: Drugs that inhibit CYP2D6 can be expected to increase plasma levels of nebivolol. When Bystolic is co-administered with an inhibitor or an inducer of this enzyme, patients should be closely monitored and the nebivolol dose adjusted according to blood pressure response. Fluoxetine, a CYP2D6 inhibitor, administered at 20 mg per day for 21 days prior to a single 10 mg dose of nebivolol to 10 healthy adults, led to an 8-fold increase in the AUC and 3-fold increase in C_{max} for d-nebivolol.

The FDA objected to the claim, “Favorable tolerability profile with a low incidence of beta blocker-related side effects.” The FDA determined that this claim implied that the tolerability profile of Bystolic is better than the tolerability profile of other β -adrenergic receptor blocking agents, when this has not been demonstrated by substantial evidence or substantial clinical experience. The FDA also objected to the claim, “Favorable tolerability profile,” stating that it minimized the risks associated with Bystolic.

Unsubstantiated Efficacy Claims

The FDA objected to the claim, “Efficacy demonstrated across a broad range of patients.” The FDA stated that the cited claim implied that efficacy was demonstrated within each subgroup (obese, poor metabolizers, and diabetic) presented in conjunction with this claim, when this has not been supported by substantial evidence or substantial clinical experience. None of the efficacy trials for Bystolic were specifically designed to evaluate effectiveness in patients who were obese, poor metabolizers, or diabetic. The FDA is not aware of any studies with Bystolic demonstrating efficacy in the above referenced subgroups. Effectiveness was established in black hypertensive patients and was similar in subgroups analyzed by age and sex.

Important Safety Information

Patients being treated with Bystolic should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported following the abrupt cessation of therapy with beta blockers. When discontinuation is planned, the dosage should be reduced gradually over a 1- to 2-week period and the patient carefully monitored.

Bystolic is contraindicated in severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place), severe hepatic impairment (Child-Pugh $>B$), and in patients who are hypersensitive to any component of this product.

Bystolic should be used with caution in patients with peripheral vascular disease, thyrotoxicosis, in patients treated concomitantly with beta blockers and calcium channel blockers of the verapamil and diltiazem type (ECG and blood pressure should be monitored), severe renal impairment, and any degree of hepatic impairment or in patients undergoing major surgery. In patients who have compensated congestive heart failure, Bystolic should be administered cautiously. If heart failure worsens, discontinuation of Bystolic should be considered. Caution should also be used in diabetic patients as beta blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia.

When Bystolic is administered with CYP2D6 inhibitors such as fluoxetine, significant increases in d-nebivolol may be observed (ie, an 8-fold increase in AUC).

In general, patients with bronchospastic disease should not receive beta blockers.

Bystolic should not be combined with other beta blockers.

The most common adverse events with Bystolic versus placebo (approximately $\geq 1\%$ and greater than placebo) were headache, fatigue, dizziness, diarrhea, nausea, insomnia, chest pain, bradycardia, dyspnea, rash, and peripheral edema.

Please see the accompanying brief summary of Prescribing Information for full risk information.



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