

Intrarenal Fenoldopam May Protect Kidneys

BY MITCHEL L. ZOLER

HOLLYWOOD, FLA. — Targeted renal therapy with the vasodilating drug fenoldopam was effective for treating acute kidney injury and for preventing contrast-induced nephropathy in results from a pair of studies.

By infusing the drug directly into patients' renal arteries with a specially designed catheter, targeted therapy allows

the use of a substantial dose of fenoldopam mesylate while avoiding systemic adverse effects such as hypotension, Dr. James A. Tumlin said at ISET 2009, an international symposium on endovascular therapy.

He reported treating a series of 28 patients with oliguria and diuretic-unresponsive acute kidney injury. Their average serum creatinine level at entry into the study was about 1.7 mg/dL. Many of

the patients had one or more comorbidities, with 57% having respiratory distress, 46% on mechanical ventilation, 43% having sepsis, and 39% with a left ventricular ejection fraction less than 35%.

All patients received intrarenal fenoldopam via a Benephit peripheral vascular catheter made by FlowMedica Inc. The catheter is designed to infuse both renal arteries with a single device, and was approved by the Food and Drug

Administration in late 2008 for targeted renal therapy in patients at risk for developing acute kidney injury. Dr. Tumlin is a consultant to and has received grant support from FlowMedica.

Their goal dosage was a fenoldopam infusion of 0.4 mcg/kg per minute, and the actual average dose used was 0.39 mcg/kg per minute, with a maximum dose given to any patient of 0.8 mcg/kg per minute. The target duration of treatment was 48 hours, and the actual average duration was 42 hours, with a maximum of 72 hours.

Renal recovery, defined as a fall in serum creatinine, occurred in 17 patients (61%) by the fourth day after treatment, and in 27 (96%) of patients by a week after treatment. Three of the patients (11%) died during follow-up, and another four patients (14%) required dialysis during follow-up. (None of the dialysis patients died.) "This was an unusually low mortality rate" compared with the

Bystolic 
(nebivolol) Tablets

2.5 mg, 5 mg, 10 mg and 20 mg

Rx Only

Brief Summary: For complete details please see full Prescribing Information for BYSTOLIC.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

WARNINGS

Abrupt Cessation of Therapy

Patients with coronary artery disease 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 in patients with coronary artery disease following the abrupt discontinuation of therapy with β -blockers. Myocardial infarction and ventricular arrhythmias may occur with or without preceding exacerbation of the angina pectoris. Even patients without overt coronary artery disease should be cautioned against interruption or abrupt discontinuation of therapy. As with other β -blockers, when discontinuation of BYSTOLIC is planned, patients should be carefully observed and advised to minimize physical activity. BYSTOLIC should be tapered over 1 to 2 weeks when possible. If the angina worsens or acute coronary insufficiency develops, it is recommended that BYSTOLIC be promptly reinstated, at least temporarily.

Cardiac Failure

Sympathetic stimulation is a vital component supporting circulatory function in the setting of congestive heart failure, and β -blockade may result in further depression of myocardial contractility and precipitate more severe failure. In patients who have compensated congestive heart failure, BYSTOLIC should be administered cautiously. If heart failure worsens, discontinuation of BYSTOLIC should be considered.

Angina and Acute Myocardial Infarction

BYSTOLIC was not studied in patients with angina pectoris or who had a recent MI.

Bronchospastic Diseases

In general, patients with bronchospastic diseases should not receive β -blockers.

Anesthesia and Major Surgery

If BYSTOLIC is to be continued perioperatively, patients should be closely monitored when anesthetic agents which depress myocardial function, such as ether, cyclopropane, and trichloroethylene, are used. If β -blocking therapy is withdrawn prior to major surgery, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

The β -blocking effects of BYSTOLIC can be reversed by β -agonists, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Additionally, difficulty in restarting and maintaining the heartbeat has been reported with β -blockers.

Diabetes and Hypoglycemia

β -blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nonselective β -blockers may potentiate insulin-induced hypoglycemia and delay recovery of serum glucose levels. It is not known whether nebivolol has these effects. Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, should be advised about these possibilities and nebivolol should be used with caution.

Thyrototoxicosis

β -blockers may mask clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of β -blockers may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate a thyroid storm.

Peripheral Vascular Disease

β -blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in these patients.

Non-dihydropyridine Calcium Channel Blockers

Because of significant negative inotropic and chronotropic effects in patients treated with β -blockers and calcium channel blockers of the verapamil and diltiazem type, caution should be used in patients treated concomitantly with these agents and ECG and blood pressure should be monitored.

PRECAUTIONS

Use with CYP2D6 Inhibitors

Nebivolol exposure increases with inhibition of CYP2D6 (see Drug Interactions). The dose of BYSTOLIC may need to be reduced.

Impaired Renal Function

BYSTOLIC should be used with caution in patients with severe renal impairment because of decreased renal clearance. BYSTOLIC has not been studied in patients receiving dialysis.

Impaired Hepatic Function

BYSTOLIC should be used with caution in patients with moderate hepatic impairment because of decreased metabolism. Since BYSTOLIC has not been studied in patients with severe hepatic impairment, BYSTOLIC is contraindicated in this population (see CLINICAL PHARMACOLOGY, Special Populations and DOSAGE AND ADMINISTRATION).

Risk of Anaphylactic Reactions

While taking β -blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reactions.

In patients with known or suspected pheochromocytoma, an α -blocker should be initiated prior to the use of any β -blocker.

Information for Patients

Patients should be advised to take BYSTOLIC regularly and continuously, as directed. BYSTOLIC can be taken with or without food. If a dose is missed, the patient should take the next scheduled dose only (without doubling it). Patients should not interrupt or discontinue BYSTOLIC without consulting the physician.

Patients should know how they react to this medicine before they operate automobiles, use machinery, or engage in other tasks requiring alertness.

Patients should be advised to consult a physician if any difficulty in breathing occurs, or if they develop signs or symptoms of worsening congestive heart failure such as weight gain or increasing shortness of breath, or excessive bradycardia.

Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, should be cautioned that β -blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nebivolol should be used with caution in these patients.

Drug Interactions

BYSTOLIC should be used with care when myocardial depressants or inhibitors of AV conduction, such as certain calcium antagonists (particularly of the phenylalkylamine [verapamil] and benzothiazepine [diltiazem] classes), or antiarrhythmic agents, such as disopyramide, are used concurrently. Both digitalis glycosides and β -blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.

BYSTOLIC should not be combined with other β -blockers. Patients receiving catecholamine-depleting drugs, such as reserpine or guanethidine, should be closely monitored, because the added β -blocking action of BYSTOLIC may produce excessive reduction of sympathetic activity. In patients who are receiving BYSTOLIC and clonidine, BYSTOLIC should be discontinued for several days before the gradual tapering of clonidine.

CYP2D6 Inhibitors: Use caution when BYSTOLIC is co-administered with CYP2D6 inhibitors (quinidine, propafenone, fluoxetine, paroxetine, etc.) (see CLINICAL PHARMACOLOGY, Drug Interactions).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a two-year study of nebivolol in mice, a statistically significant increase in the incidence of testicular Leydig cell hyperplasia and adenomas was observed at 40 mg/kg/day (5 times the maximally recommended human dose of 40 mg on a mg/m² basis). Similar findings were not reported in mice administered doses equal to approximately 0.3 or 1.2 times the maximum recommended human dose. No evidence of a tumorigenic effect was observed in a 24-month study in Wistar rats receiving doses of nebivolol 2.5, 10 and 40 mg/kg/day (equivalent to 0.6, 2.4, and 10 times the maximally recommended human dose). Co-administration of dihydrotestosterone reduced blood LH levels and prevented the Leydig cell hyperplasia, consistent with an indirect LH-mediated effect of nebivolol in mice and not thought to be clinically relevant in man.

A randomized, double-blind, placebo- and active-controlled, parallel-group study in healthy male volunteers was conducted to determine the effects of nebivolol on adrenal function, luteinizing hormone, and testosterone levels. This study demonstrated that 6 weeks of daily dosing with 10 mg of nebivolol had no significant effect on ACTH-stimulated mean serum cortisol AUC_{0-120 min}, serum LH, or serum total testosterone.

Effects on spermatogenesis were seen in male rats and mice at >40 mg/kg/day (10 and 5 times the MRHD, respectively). For rats the effects on spermatogenesis were not reversed and may have worsened during a four week recovery period. The effects of nebivolol on sperm in mice, however, were partially reversible.

Mutagenesis: Nebivolol was not genotoxic when tested in a battery of assays (Ames, *in vitro* mouse lymphoma TK⁺, *in vitro* human peripheral lymphocyte chromosome aberration, *in vivo* Drosophila melanogaster sex-linked recessive lethal, and *in vivo* mouse bone marrow micronucleus tests).

Pregnancy: Teratogenic Effects. Pregnancy Category C.

Decreased pup body weights occurred at 1.25 and 2.5 mg/kg in rats, when exposed during the perinatal period (late gestation, parturition and lactation). At 5 mg/kg and higher doses (1.2 times the MRHD), prolonged gestation, dystocia and reduced maternal care were produced with corresponding increases in late fetal deaths and stillbirths and decreased birth weight, live litter size and pup survival. Insufficient numbers of pups survived at 5 mg/kg to evaluate the offspring for reproductive performance.

In studies in which pregnant rats were given nebivolol during organogenesis, reduced fetal body weights were observed at maternally toxic doses of 20 and 40 mg/kg/day (5 and 10 times the MRHD), and small reversible delays in sternal and thoracic ossification associated with the reduced fetal body weights and a small increase in resorption occurred at 40 mg/kg/day (10 times the MRHD). No adverse effects on embryo-fetal viability, sex, weight or morphology were observed in studies in which nebivolol was given to pregnant rabbits at doses as high as 20 mg/kg/day (10 times the MRHD).

Labor and Delivery

Nebivolol caused prolonged gestation and dystocia at doses \geq 5 mg/kg in rats (1.2 times the MRHD). These effects were associated with increased fetal deaths and stillborn pups, and decreased birth weight, live litter size and pup survival rate, events that occurred only when nebivolol was given during the perinatal period (late gestation, parturition and lactation).

No studies of nebivolol were conducted in pregnant women. BYSTOLIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Studies in rats have shown that nebivolol or its metabolites cross the placental barrier and are excreted in breast milk. It is not known whether this drug is excreted in human milk.

Because of the potential for β -blockers to produce serious adverse reactions in nursing infants, especially bradycardia, BYSTOLIC is not recommended during nursing.

Geriatric Use

Of the 2800 patients in the U.S. sponsored placebo-controlled clinical hypertension studies, 478 patients were 65 years of age or older. No overall differences in efficacy or in the incidence of adverse events were observed between older and younger patients.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Pediatric studies in ages newborn to 18 years old have not been conducted because of incomplete characterization of developmental toxicity and possible adverse effects on long-term fertility (see Carcinogenesis, Mutagenesis, and Impairment of Fertility).

ADVERSE REACTIONS

The data described below reflect worldwide clinical trial exposure to BYSTOLIC in 6545 patients, including 5038 patients treated for hypertension and the remaining 1507 subjects treated for other cardiovascular diseases. Doses ranged from 0.5 mg to 40 mg. Patients received BYSTOLIC for up to 24 months, with over 1900 patients treated for at least 6 months, and approximately 1300 patients for more than one year. In placebo-controlled clinical trials comparing BYSTOLIC with placebo, discontinuation of therapy due to adverse events was reported in 2.8% of patients treated with nebivolol and 2.2% of patients given placebo. The most common adverse events that led to discontinuation of BYSTOLIC were headache (0.4%), nausea (0.2%) and bradycardia (0.2%).

Adverse Reactions in Controlled Trials

Table 1 lists treatment-emergent signs and symptoms that were reported in three 12-week, placebo-controlled monotherapy trials involving 1597 hypertensive patients treated with either 5 mg, 10 mg or 20-40 mg of BYSTOLIC and 205 patients given placebo and for which the rate of occurrence was at least 1% of patients treated with nebivolol and greater than the rate for those treated with placebo in at least one dose group.

Table 1. Treatment-Emergent Adverse Events with an Incidence (over 6 weeks) \geq 1% in BYSTOLIC-Treated Patients and at a Higher Frequency than Placebo-Treated Patients

	Placebo (n = 205) (%)	Nebivolol 5 mg (n = 459) (%)	Nebivolol 10 mg (n = 461) (%)	Nebivolol 20-40 mg (n = 677) (%)
Headache	6	9	6	7
Fatigue	1	2	2	5
Dizziness	2	2	3	4
Diarrhea	2	2	2	3
Nausea	0	1	3	2
Insomnia	0	1	1	1
Chest pain	0	0	1	1
Bradycardia	0	0	0	1
Bradypnea	0	0	1	1
Rash	0	0	1	1
Peripheral edema	0	1	1	1

Other Adverse Events Observed During Worldwide Clinical Trials

Listed below are other reported adverse events with an incidence of at least 1% in the more than 5300 patients treated with BYSTOLIC in controlled or open-label trials, whether or not attributed to treatment, except for those already appearing in Table 1, terms too general to be informative, minor symptoms, or events unlikely to be attributable to drug because they are common in the population. These adverse events were in most cases observed at a similar frequency in placebo-treated patients in the controlled studies.

Body as a Whole:

asthenia.

Gastrointestinal System Disorders:

abdominal pain

Metabolic and Nutritional Disorders:

hypercholesterolemia and hyperuricemia

Nervous System Disorders:

paraesthesia

Laboratory

In controlled monotherapy trials, BYSTOLIC was associated with an increase in BUN, uric acid, triglycerides and a decrease in HDL cholesterol and platelet count.

Events Identified from Spontaneous Reports of BYSTOLIC Received Worldwide

The following adverse events have been identified from spontaneous reports of BYSTOLIC received worldwide and have not been listed elsewhere. These adverse events have been chosen for inclusion due to a combination of seriousness, frequency of reporting or potential causal connection to BYSTOLIC. Events common in the population have generally been omitted. Because these events were reported voluntarily from a population of uncertain size, it is not possible to estimate their frequency or establish a causal relationship to BYSTOLIC exposure: abnormal hepatic function (including increased AST, ALT and bilirubin), acute pulmonary edema, acute renal failure, atrioventricular block (both second and third degree), bronchospasm, erectile dysfunction, hypersensitivity (including urticaria, allergic vasculitis and rare reports of angioedema), myocardial infarction, pruritus, psoriasis, Raynaud's phenomenon, peripheral ischemia/claudecaudation, somnolence, syncope, thrombocytopenia, various rashes and skin disorders, vertigo, and vomiting.

OVERDOSAGE

In clinical trials and worldwide postmarketing experience there were reports of BYSTOLIC overdose. The most common signs and symptoms associated with BYSTOLIC overdose are bradycardia and hypotension. Other important adverse events reported with BYSTOLIC overdose include cardiac failure, dizziness, hypoglycemia, fatigue and vomiting. Other adverse events associated with β -blocker overdose include bronchospasm and heart block.

The largest known ingestion of BYSTOLIC worldwide involved a patient who ingested up to 500 mg of BYSTOLIC along with several 100 mg tablets of acetylsalicylic acid in a suicide attempt. The patient experienced hyperhidrosis, pallor, depressed level of consciousness, hypokinesia, hypotension, sinus bradycardia, hypoglycemia, hypokalemia, respiratory failure and vomiting. The patient recovered.

Due to extensive drug binding to plasma proteins, hemodialysis is not expected to enhance nebivolol clearance.

If overdose occurs, BYSTOLIC should be stopped and general supportive and specific symptomatic treatment should be provided. Based on expected pharmacologic actions and recommendations for other β -blockers, the following general measures should be considered when clinically warranted:

Bradycardia: Administer IV atropine. If the response is inadequate, isoproterenol or another agent with positive chronotropic properties may be given cautiously. Under some circumstances, transthoracic or transvenous pacemaker placement may be necessary.

Hypotension: Administer IV fluids and vasopressors. Intravenous glucagon may be useful.

Heart Block (second or third degree): Patients should be carefully monitored and treated with isoproterenol infusion. Under some circumstances, transthoracic or transvenous pacemaker placement may be necessary.

Congestive Heart Failure: Initiate therapy with digitalis glycoside and diuretics. In certain cases, consideration should be given to the use of inotropic and vasodilating agents.

Bronchospasm: Administer bronchodilator therapy such as a short acting inhaled β_2 -agonist and/or aminophylline.

Hypoglycemia: Administer IV glucose. Repeated doses of IV glucose or possibly glucagon may be required.

In the event of intoxication where there are symptoms of shock, treatment must be continued for a sufficiently long period consistent with the 12-19 hour effective half-life of BYSTOLIC. Supportive measures should continue until clinical stability is achieved.

Call the National Poison Control Center (800-222-1222) for the most current information on β -blocker overdose treatment.

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Targeted therapy allows the use of a substantial dose of fenoldopam while avoiding systemic adverse effects.

DR. TUMLIN

historic experience with similar patients who did not undergo renal infusion with fenoldopam, said Dr. Tumlin, a nephrologist and professor of medicine at the University of Tennessee in Chattanooga.

The second experience using intrarenal fenoldopam presented at the meeting included data from 593 patients who were enrolled in a targeted renal therapy registry. The series included 340 patients who were treated to prevent contrast-induced nephropathy and another 40 patients who were treated for acute kidney injury that they developed following coronary artery bypass grafting.

Intrarenal fenoldopam was given to 94% of the registry's patients, at a median dosage of 0.4 mcg/kg per minute, with a range of 0.05-0.8 mcg/kg per minute. The remaining patients received another drug, such as sodium bicarbonate, reported Dr. John H. Rundback in a separate talk. The median duration of the fenoldopam infusion was 180 min.

Bilateral renal-artery catheterization was performed successfully in 95% of the registry patients, a procedure that took an average of 2 minutes.

The registry outcomes showed that the 0.4 mcg/kg per minute dosage was much more effective than was a 0.2-mcg/kg per minute dosage for preventing contrast-induced nephropathy, and that treatment for at least an hour was more effective than a briefer infusion, said Dr. Rundback, an interventional radiologist and director of the Interventional Institute at Holy Name Hospital in Teaneck, N.J. Dr. Rundback has been a consultant to and a member of the scientific advisory board of FlowMedica. ■