

Flat-Panels Cut Contrast, Yield Better Results

BY MITCHEL L. ZOLER

HOLLYWOOD, FLA. — Flat-panel detector systems have made it possible to perform angiography with a quarter of the contrast media routinely used with conventional image intensifiers.

“Flat-panel systems represent a huge evolution in angiographic technology,” Dr. Timothy W. Clark said at ISET 2009, an international symposium on endovascular therapy. “Much less contrast is needed to generate the same image quality as conventional image intensifiers, and because image production is more efficient, there is less radiation exposure to patients” and staff, said Dr. Clark, chief of vascular and interventional radiology at New York University. The reduction cuts the risk for contrast-induced nephropathy.

Flat panels offer a “dramatically wider dynamic range across all soft tissue anatomy, a larger field of view, homogeneous and distortion-free images,

and improved detector efficiency,” he said. These features improve visualization, despite less contrast and a lower radiation dose. Unlike conventional image intensifiers, they do not involve an analog conversion, there is no geometric distortion, and there is no lateral dispersion of light to reduce image sharpness. Flat panels are less bulky and allow for greater freedom of movement.

With a flat-panel detector, Dr. Clark uses iodinated contrast diluted to 25%.

The degree of dilution depends on the contrast resolution of the flat-panel system.

For renal arteriograms, he said he has produced excellent images using a total contrast volume of 7 mL. For renal stenting, he uses 15 mL. For a popliteal chronic total occlusion, he uses a total volume of 25 mL, and for an iliac chronic total

occlusion, he uses 32 mL of contrast.

“We use amazingly small volumes of contrast and still get high-resolution images,” said Dr. Clark, who does not have financial relationships with the companies that make flat-panel detectors.

One caveat regarding the use of diluted contrast is that the fluid must be power injected so it can displace the blood within the imaged vessels, he said. ■

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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FDA: Remove Drug Patches Before MRIs

To eliminate any risk of skin burns, transdermal medication patches should be removed before patients undergo magnetic resonance imaging scans, the Food and Drug Administration advises.

Prompted by less than half a dozen reports of burns associated with patches that contain trace amounts of aluminum or other metals, the FDA issued a public health advisory in March. The burns, reported in nicotine patches, have been described as similar to a “serious sunburn,” Dr. Sandra Kweder, deputy director of the FDA's Office of New Drugs, said during a telebriefing.

The advisory applies to all patches, even those without metals, because not all patches carry a warning about the risk, and metal may not be visible. Clinicians should instruct patients about when to remove patches before procedures and about replacing them afterward, the advisory said.

About 60 medicated patches are on the market. Uses include smoking cessation, contraception, hormone therapy, and pain treatment.

More than 25% of them contain metal, Dr. Kweder said. Even transparent patches may contain metals.

The FDA is reviewing the labeling and composition of all transdermal medication patches, and is working with manufacturers to improve labeling, which could include some type of warning on the patch.

—Elizabeth Mehcatic

The advisory is available online at www.fda.gov/medwatch/safety/2009/safety09.htm#Transdermal.