Heart Rate Response Predicts Postpartum Events

BY MITCHEL L. ZOLER

ORLANDO — Chronotropic index, a measure of heart rate response in an exercise test, significantly correlated with the risk for postpartum adverse cardiac events in a review of 83 women with congenital heart disease.

The finding shows that chronotropic index can provide valuable guidance when counseling women with congenital heart disease about the risk they face from pregnancy for triggering a cardiac or neonatal event, Dr. George K. Lui said at the annual scientific sessions of the American Heart Association.

The chronotropic index "is a helpful tool," along with other risk markers such as a history of heart failure or of sustained arrhythmias, said Dr. Lui, director of adult congenital heart disease at Montefiore Medical Center in the Bronx, N.Y. "Stress testing adds to the risk assessment and counseling," of these women, "especially in patients at borderline risk," he said in an interview.

His study used data collected through the Alliance for Adult Research in Congenital Cardiology at 13 centers in the United States and Canada.

The 83 women had undergone a cardiopulmonary exercise test within the period starting 2 years prior to their pregnancy and running through the end of their first trimester. Their average age was 29 years, 88% had New York Heart Association class I heart failure, 12% had class II symptoms, and none were cyanotic.

The most common congenital heart disease was repaired tetralogy of Fallot, in 35%; D-transposition of the great arteries, in 29%; left-sided obstruction le-

administration of subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 ml) and measures to ensure a patent airway may be necessary.

Discontinue aliskiren immediately in patients who develop angioedema and do not readminister.

5.3 Hypotension
An excessive fall in blood pressure (hypotension) was rarely seen (<0.5%) in patients with uncomplicated hypertension treated with Valturna in controlled trials.

In patients with an activated renin-angiotensin-aldosterone system, such as volume- or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur in patients receiving renin-angiotensin-aldosterone system (RAAS) blockers. Correct these conditions prior to the administration of Valturna, or start the treatment under close medical supervision.

Initiate therapy cautiously in patients with heart failure or recent myocardial infarction and in patients undergoing surgery or dialysis. Patients with heart failure or post-myocardial infarction patients given valsartan commonly have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed. In controlled trials in heart failure patients, the incidence of hypotension in valsartan-treated patients was 5.5% compared to 1.8% in placebo-treated patients. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), hypotension in post-myocardial infarction patients led to permanent discontinuation of therapy in 1.4% of valsartan-treated patients and 0.8% of captopril-treated patients.

If an excessive fall in blood pressure occurs with Valturna, place the patient in the supine position and, if necessary, give an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

5.4 Patients with Severe Renal Impairment
Valturna
Patients with severe renal impairment were excluded from clinical trials with Valturna in hypertension.

Aliskiren
Patients with severe renal dysfunction (creatinine 1.7 mg/dL for women and 2.0 mg/dL for men and/or estimated GFR <30 mL/min), a history of dialysis, nephrotic syndrome, or renovascular hypertension were excluded from clinical trials of aliskiren in hypertension. Safety information with aliskiren and the potential for other drugs acting on the renin-angiotensin-aldosterone system to increase serum creatinine and blood urea nitrogen are not available.

Valsartan
In studies of ACE inhibitors in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4-day trial of valsartan in 12 hypertensive patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of valsartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may occur particularly in volume depleted patients. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria or progressive azotemia and (rarely) with acute renal failure or death. Similar outcomes have been reported with valsartan.

5.5 Patients with Hepatic Impairment
Valsartan
As the majority of valsartan is eliminated in the bile, patients with mild-to-moderate hepatic impairment, including patients with biliary obstructive disorders, showed lower valsartan clearance (higher AUCs).

5.6 Patients with Congestive Heart Failure and Post-Myocardial Infarction
Valsartan
Some patients with heart failure have developed increases in blood urea nitrogen, serum creatinine, and potassium on valsartan. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or valsartan may be required. In the Valsartan Heart Failure Trial, in which 93% of patients were on concomitant ACE inhibitors, treatment was discontinued for elevations in creatinine or potassium (total of 1.0% on valsartan vs. 0.2% on placebo). In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), discontinuation due to various types of renal dysfunction occurred in 1.1% of valsartan-treated patients and 0.8% of captopril-treated patients. Include assessment of renal function when evaluating patients with heart failure or post-myocardial infarction.

5.7 Serum Electrolyte Abnormalities
Valturna
In the short-term controlled trials of various doses of Valturna, the incidence of hyperkalemia (serum potassium >5.5 mEq/L) was about 1%-2% higher in the combination treatment group compared with the monotherapies aliskiren and valsartan, or with placebo.

In a long-term, uncontrolled study with median treatment duration of about one year, about 4% of the patients had at least one serum potassium >5.5 mEq/L at some time during the study; about 0.8% of patients discontinued study treatment and had a high serum potassium at some point during the study. Patients with hyperkalemia were older (median age 65 vs. 55) with slightly lower mean baseline estimated creatinine clearance compared to patients without hyperkalemia. While about 25% of the hyperkalemic episodes occurred in the first two months, other initial episodes were reported throughout the study.

Periodic determinations of serum electrolytes to detect possible electrolyte imbalances is advised, particularly in patients at risk for hyperkalemia such as those with renal impairment.

Caution is advised with concomitant use of Valturna with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other drugs that increase potassium levels may lead to increases in serum potassium.

5.8 Renal Artery Stenosis
Aliskiren
No data are available on the use of aliskiren in patients with unilateral or bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Valsartan
In studies of ACE inhibitors in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4-day trial of valsartan in 12 hypertensive patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of valsartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.

5.9 Cyclosporine
Aliskiren
When aliskiren was given with cyclosporine, the blood concentrations of aliskiren were significantly increased. Concomitant use of aliskiren with cyclosporine is not recommended *[see Drug Interactions (7)]*.

6 ADVERSE REACTIONS
6.1 Clinical Studies Experience
The following serious adverse reactions are discussed in greater detail in other sections of the label:
- Risk of fetal/neonatal morbidity and mortality *[see Warnings and Precautions (5.1)]*
- Head and neck angioedema *[see Warnings and Precautions (5.2)]*
- Hypotension *[see Warnings and Precautions (5.3)]*

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice.

Valturna
Valturna has been evaluated for safety in more than 1,225 patients, including over 316 patients for over 1 year. In placebo-controlled clinical trials, discontinuation of therapy because of a clinical adverse event (including uncontrolled hypertension) occurred in 1.4% of patients treated with Valturna versus 2.7% of patients given placebo.

Adverse events in placebo-controlled trials that occurred in at least 1% of patients treated with Valturna and at a higher incidence than placebo included fatigue (2.6% vs. 1.4%), nasopharyngitis (2.6% vs. 2.2%), diarrhea (1.4% vs 0.9%), upper respiratory tract infection (1.4% vs. 1.1%), urinary tract infection (1.4% vs. 0.6%), influenza (1.1% vs 0.2%), and vertigo (1.1% vs. 0.3%).

Hyperkalemia has been observed as a serum electrolyte abnormality in Valturna clinical trials *[see Warnings and Precautions (5.7)]*.

sions, in 11%; and right-sided obstructive lesions, in 10%.

The study included outcomes from the 89 pregnancies.

The chronotropic index calculation involved subtracting a woman's resting heart rate from her peak exercise heart rate and dividing the difference by 220 minus her age and minus her resting heart rate.

According to a survey of healthy adults published in 1989, normal chronotropic index is 1.0, with a normal range of 0.8-1.3 (J. Cardiovasc. Electrophysiol. 1989;3:176-80).

The women in Dr. Lui's study had an average chronotropic index of 0.75. More than half had a chronotropic index below the normal range cutoff of 0.80.

Women who had a chronotropic index of less than 0.80 had an increased risk for cardiac and neonatal events.

DR. LUI

During pregnancy, 15 of the women had a cardiac event, including 12 with heart failure, 6 with a sustained arrhythmia, and 1 death. Also, among the 89 pregnancies were 17 neonatal events, including 16 preterm deliveries, 7 neonates who were small for gestational age, and 3 episodes of respiratory distress syndrome.

Women who had a chronotropic index of less than 0.80 had a significantly increased risk for both a cardiac event and neonatal event.

A univariate analysis indicated that women with a chronotropic index of 0.80 or higher were 35% less likely to have a cardiac event and their pregnancies were 27% less likely to have a neonatal event, compared with women with a chronotropic index of less than 0.80.

Results of multivariate analysis that controlled for treatment with an antiarrhythmic medication showed that a chronotropic index of 0.80 or higher lowered the risk for a maternal cardiac event by 30%.

Dr. Lui stated that he had no financial disclosures. ■

Aliskiren

Aliskiren has been evaluated for safety in 6,460 patients, including 1,740 treated for longer than 6 months, and 1,250 for longer than 1 year. In placebo-controlled clinical trials, discontinuation of therapy because of a clinical adverse event, including uncontrolled hypertension occurred in 2.2% of patients treated with aliskiren, versus 3.5% of patients given placebo.

Two cases of angioedema with respiratory symptoms were reported with aliskiren use in the clinical studies. Two other cases of periorbital edema without respiratory symptoms were reported as possible angioedema and resulted in discontinuation. The rate of these angioedema cases in the completed studies was 0.06%.

In addition, 26 other cases of edema involving the face, hands, or whole body were reported with aliskiren use, including 4 leading to discontinuation.

In the placebo-controlled studies, however, the incidence of edema involving the face, hands, or whole body was 0.4% with aliskiren compared with 0.5% with placebo. In a long-term active-controlled study with aliskiren and HCTZ arms, the incidence of edema involving the face, hands, or whole body was 0.4% in both treatment arms.

Aliskiren produces dose-related gastrointestinal (GI) adverse reactions. Diarrhea was reported by 2.3% of patients at 300 mg, compared to 1.2% in placebo patients. In women and the elderly (age ≥65) increases in diarrhea rates were evident starting at a dose of 150 mg daily, with rates for these subgroups at 150 mg similar to those seen at 300 mg for men or younger patients (all rates about 2%). Other GI symptoms included abdominal pain, dyspepsia, and gastroesophageal reflux, although increased rates for abdominal pain and dyspepsia were distinguished from placebo only at 600 mg daily. Diarrhea and other GI symptoms were typically mild and rarely led to discontinuation.

Aliskiren was associated with a slight increase in cough in the placebo-controlled studies (1.1% for any aliskiren use vs. 0.6% for placebo). In active-controlled trials with ACE inhibitor (ramipril, lisinopril) arms, the rates of cough for the aliskiren arms were about one-third to one-half the rates in the ACE inhibitor arms.

Other adverse reactions with increased rates for aliskiren compared to placebo included rash (1% vs. 0.3%), elevated uric acid (0.4% vs. 0.1%), gout (0.2% vs. 0.1%), and renal stones (0.2% vs. 0%).

Single episodes of tonic-clonic seizures with loss of consciousness were reported in two patients treated with aliskiren in the clinical trials. One patient had predisposing causes for seizures and had a negative electroencephalogram (EEG) and cerebral imaging following the seizures; for the other patient, EEG and imaging results were not reported. Aliskiren was discontinued and there was no rechallenge in either case.

The following adverse events occurred in placebo-controlled clinical trials at an incidence of more than 1% of patients treated with aliskiren, but also occurred at about the same or greater incidence in patients receiving placebo: headache, nasopharyngitis, dizziness, fatigue, upper respiratory tract infection, back pain and cough.

No clinically meaningful changes in vital signs or in ECG (including QTc interval) were observed in patients treated with aliskiren.

Valsartan

Valsartan has been evaluated for safety in more than 4,000 hypertensive patients in clinical trials, including over 400 treated for over 6 months, and more than 160 for over 1 year.

In trials in which valsartan was compared to an ACE inhibitor with or without placebo, the incidence of dry cough was significantly greater in the ACE inhibitor group (7.9%) than in the groups who received valsartan (2.6%) or placebo (1.5%). In a 129 patient trial limited to patients who had had dry cough when they had previously received ACE inhibitors, the incidences of cough in patients who received valsartan, HCTZ, or lisinopril were 20%, 19%, and 69% respectively ($p<0.001$).

Other adverse reactions, not listed above, occurring in >0.2% of patients in controlled clinical trials with valsartan are:

Body as a Whole: allergic reaction, asthenia

Musculoskeletal: muscle cramps

Neurologic and Psychiatric: paresthesia

Respiratory: sinusitis, pharyngitis

Urogenital: impotence

Other reported events seen less frequently in clinical trials were: angioedema.

Adverse reactions reported for valsartan for indications other than hypertension may be found in the prescribing information for Diovan.

6.2 Clinical Laboratory Test Abnormalities

RBC count, hemoglobin and hematocrit:

Small mean decreases from baseline were seen in RBC count, hemoglobin and hematocrit in both monotherapies and combination therapy. These changes were small, but changes in hemoglobin were slightly more pronounced with the combination therapy (-0.26 g/dL) than with monotherapy regimens (-0.04 g/dL in aliskiren or -0.13 g/dL in valsartan) or placebo (+0.07 g/dL).

Blood Urea Nitrogen (BUN)/Creatinine:

Elevations in BUN (>40 mg/dL) and creatinine (>2.0 mg/dL) in any treatment group were less than 1.0%. For creatinine, 0.5% (3/599) of patients on combination treatment had a creatinine level >1.5 mg/dL at the end of the study and a 30% increase from baseline compared to none in either monotherapy or placebo.

Serum Electrolytes: See Warnings and Precautions (5.7)

7 DRUG INTERACTIONS

No drug interaction studies have been conducted with Valturna and other drugs, although studies with the individual aliskiren and valsartan components are described below.

Aliskiren

Effects of Other Drugs on Aliskiren

Based on *in vitro* studies, aliskiren is metabolized by CYP 3A4.

Irbesartan: Coadministration of irbesartan reduced aliskiren C_{max} up to 50% after multiple dosing.

P-glycoprotein Effects: Pgp (MDR1/Mdr1a/1b) was found to be the major efflux system involved in absorption and disposition of aliskiren in preclinical studies. The potential for drug interactions at the Pgp site will likely depend on the degree of inhibition of this transporter. Coadministration of aliskiren with Pgp substrates or weak to moderate inhibitors such as atenolol, digoxin, and amlodipine did not result in clinically relevant interactions.

Atorvastatin: Coadministration of atorvastatin resulted in about a 50% increase in aliskiren C_{max} and AUC after multiple dosing.

Ketoconazole: Coadministration of 200 mg twice-daily ketoconazole, a potent Pgp inhibitor, with aliskiren resulted in approximate 80% increase in plasma levels of aliskiren. A 400-mg once-daily dose was not studied but would be expected to increase aliskiren blood levels further.

Cyclosporine: Coadministration of 200 mg and 600 mg cyclosporine, a highly potent Pgp inhibitor, with 75 mg aliskiren resulted in an approximately 2.5-fold increase in C_{max} and 5-fold increase in AUC of aliskiren. Concomitant use of aliskiren with cyclosporine is not recommended.

Drugs with no clinically significant effects: Coadministration of lovastatin, atenolol, warfarin, furosemide, digoxin, celecoxib, hydrochlorothiazide, ramipril, valsartan, metformin and amlodipine did not result in clinically significant increases in aliskiren exposure.

Effects of Aliskiren on Other Drugs

Aliskiren does not inhibit the CYP450 isoenzymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1, and CYP 3A) or induce CYP 3A4.

Furosemide: When aliskiren was coadministered with furosemide, the AUC and C_{max} of furosemide were reduced by about 30% and 50%, respectively. Patients receiving furosemide could find its effect diminished after starting aliskiren.

Drugs with no clinically significant effects: Coadministration of aliskiren did not significantly affect the pharmacokinetics of lovastatin, digoxin, valsartan, amlodipine, metformin, celecoxib, atenolol, atorvastatin, ramipril or hydrochlorothiazide.

Warfarin: The effects of aliskiren on warfarin pharmacokinetics have not been evaluated.

Valsartan

No clinically significant pharmacokinetic interactions were observed when valsartan was coadministered with aliskiren, amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. The valsartan-atenolol combination was more antihypertensive than either component, but it did not lower the heart rate more than atenolol alone.

Warfarin: Coadministration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.