Labetalol Use Appears Safe During Pregnancy

BY SHERRY BOSCHERT

FROM THE ANNUAL MEETING OF THE
AMERICAN COLLEGE OF
OBSTETRICIANS AND GYNECOLOGISTS
SAN FRANCISCO — Results of non-
stress tests in 112 pregnant women being treated with labetalol from January 2003 to September 2007 did not differ significantly in patients on labetalol, compared with those on methyldopa, results of a retrospective study found.

“Attending physicians should feel comfortable using labetalol or methyldopa for pregnant patients with hypertension. Those medications have no effect on the baby,” Dr. Ramata Niang said in an interview at her prize-winning poster presentation at the annual meeting of the American College of Obstetricians and Gynecologists.

Nonstress tests were reactive in 84% of 76 patients on labetalol and in 81% of 36 patients on methyldopa, a difference that was not statistically significant, reported Dr. Niang, an ob/gyn, at the University of Illinois at Chicago.

The investigators used the average of each patient’s nonstress test results to categorize results as reactive or nonreactive.

The study started with charts on 188 women. “The most common indication for hypertension was pregnancy and excluded women with multiple-gestation pregnancies, other antihypertensive treatment, or incomplete prenatal testing charts, to focus on the remaining 112 patients.”

Among secondary outcomes, there were no significant differences between the two treatment groups in maternal age (29 years for women on labetalol and 31 years for those on methyldopa), gestational age (38 weeks), birth weight (2,832 g and 3,048 g), or the rate of preeclampsia (less than 1% in both groups).

<table>
<thead>
<tr>
<th>Study of Sitagliptin and Metformin in Patients Inadequately Controlled on Diet and Exercise</th>
<th>Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>176</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>175</td>
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</tbody>
</table>

### Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Alone

**Background**

In a 24-week placebo-controlled study of sitagliptin 100 mg administered once daily as a twice daily, it was noted that no adverse reactions were noted in patients given placebo. Discontinuation of therapy due to clinical adverse reactions was similar to the placebo treatment group (sitting and meal) and more commonly in patients treated with placebo.

**Gastrointestinal Adverse Reactions**

The incidences of pre-selected gastrointestinal adverse experiences in patients treated with sitagliptin and metformin were similar to those reported for patients treated with metformin alone.

**Conclusions**

Sitagliptin had minimal effects on nifedipine and metformin plasma levels and food concentrations and a 40% increase in plasma and white blood cell count. In the study of sitagliptin and add-on combination therapy with metformin and rosiglitazone, the overall incidence of adverse reactions of hypoglycemia was 1.3% in patients given add-on sitagliptin and 2.1% in patients given add-on placebo.

In all (N=5) studies, adverse reactions of hypoglycemia were defined as symptomatic hypoglycemia that was accompanied by a blood glucose measurement ≤70 mg/dL. The combination of sitagliptin and metformin was co-administered in a 12-hour period at the recommended dosage of 25 mg/day and 52.5 mg/day, respectively. Adjustment of dosage of hypoglycemia was higher than that observed with placebo and metformin co-administered with a sulfonylurea or with insulin.

The overall incidence of reported adverse reactions of hypoglycemia in patients with type 2 diabetes inadequately controlled on diet and exercise was 6.5% in patients given placebo, 6.5% in patients given sitagliptin alone; 8.8% in patients given metformin alone, 6.1% in patients given sitagliptin in combination with metformin. In patients with type 2 diabetes inadequately controlled on metformin alone, the overall incidence of adverse reactions of hypoglycemia was 1.3% in patients given sitagliptin and 2.1% in patients given add-on placebo.

In the study of sitagliptin and metformin alone, the overall incidence of hypoglycemia was 2.2% in patients given sitagliptin plus 0.0% in patients given add-on placebos. In the study of sitagliptin and metformin, the overall incidence of hypoglycemia was 3.5% in patients given sitagliptin and 1.6% in patients given add-on placebo. With the combination of sitagliptin and metformin, no clinically meaningful changes in vital signs or in ECG (including in QTc intervals) were observed.

The most common adverse experience in sitagliptin monotherapy reported regardless of investigator assessment of causality was nausea and vomiting. In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of white blood cell count (approximately 200 cells/µL difference in WBC vs placebo; mean baseline WBC approximately 9,500) was noted in 1.9% of patients treated with sitagliptin and metformin, 1.9% of patients treated with placebo and metformin, 2.5% of patients treated with placebo.

**Conclusion**

No data were available about the interaction of metformin and furosemide when co-administered chronically. The Use of Metformin with Other Drugs. Certain drugs tend to produce hypoglycemia and may lead to loss of glucose control.

In healthy volunteers, the pharmacokinetics of sitagliptin and metformin were not affected by co-administration of sitagliptin and metformin. The most common adverse reaction due to sitagliptin was hypoglycemia, which was more commonly reported in patients treated with metformin than in patients treated with placebo.

### Sitagliptin in Combination with Metformin and Insulin

In a single-dose interaction study in normal healthy volunteers demonstrated that co-administration of rosiglitazone increased plasma metformin [Cmax and AUC] by 20% and 5%, respectively, and increased the amount excreted in the urine. Labetalol and labetalol hydrochloride are extensively bound to serum proteins.

### Pregnancy and Lactation

**Pregnancy Category C**

JANUMET are not adequate and well-controlled studies in pregnant women with JANUMET in its individual components. Therefore, the safety of JANUMET in pregnant women is not known. JANUMET should be used during pregnancy only if clearly needed.

In a single-dose interaction study in healthy volunteers, labetalol had no effect on the pharmacokinetics of sitagliptin and metformin. In healthy volunteers, labetalol had no effect on the pharmacokinetics of sitagliptin and metformin.

### Nursing Mothers

Labetalol is not teratogenic in rats and rabbits at doses up to 600 mg/kg. This represents an exposure of about 2 and 6 times the maximum recommended human daily dose of 200 mg based on body surface area to rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to labetalol.

Nursing Mothers. No studies in lactating animals have been conducted with the combined components of JANUMET in single-dose studies with the individual components, with the exception of labetalol in multiple-gestation pregnancies.

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### Footnotes

Several changes were included in the food and drink categories in the diet treatment group. The study started with charts on 188 women on labetalol and 112 patients on methyldopa, a difference that was not statistically significant, reported Dr. Niang, an ob/gyn, at the University of Illinois at Chicago.

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