Intervention Aids Insulin-Sensitive Obese Children

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BOSTON — Participation in a structured lifestyle and exercise intervention can significantly improve the metabolic parameters of obese children with high insulin sensitivity, according to findings of a study presented at the Fifth Annual World Congress on the Insulin Resistance Syndrome.

Dr. Radhika Purushothaman of the Infants' and Children's Hospital of Brooklyn (N.Y.) at Maimonides and her colleagues enrolled 128 healthy seventh-grade students into a 12-week randomized controlled trial: 24 of the students were randomized to a lifestyle-only intervention, which focused primarily on dietary modification; 58 were randomized to a lifestyle plus exercise intervention; and 46 were in a control group with no intervention. The lifestyle plus exercise group was further subdivided according to body mass index (BMI) percentile: 28 students were in the lean group (BMI less than 85%), 8 were in the overweight group (BMI between 85% and 95%), and 22 were in the obese group (BMI greater than 95%). The weight categories in this study differ from those of the Centers for Disease Control and Prevention.

Because of the small number of children in the overweight subgroup, they were not included in the final subgroup comparison.

The investigators measured clinical and biochemical parameters including height, weight, blood pressure, body fat percentage, waist circumference, lipid profile, glucose tolerance via intravenous glucose tolerance test, insulinlike growth factor binding protein-I (IGFBP-1), baseline adiponectin level, acute insulin response, quantitative insulin sensitivity check index (QUICKI), and glucose disposition index.

An assessment of the BMI subgroups of the lifestyle and exercise intervention group showed the most interesting findings. Post intervention, both subgroups demonstrated increased BMI and decreased blood pressure. Within the obese group, higher insulin sensitivity at baseline was associated with more significant loss of visceral fat, said Dr. Purushothaman.

The lean subgroup had—at baseline and post intervention—a lower percent body fat, waist circumference, systolic blood pressure, fasting insulin and acute insulin response, and a higher adiponectin level than the obese group. Relative to the obese group, the lean group showed improvements in body fat percentage, blood pressure, IGF-BP-1, acute insulin response, and glucose disposition index.

The data suggest that improvement in biochemical parameters can occur even before changes in BMI, and may be associated with a decrease in body fat percentage.

The results showed a significant negative correlation between fasting insulin at baseline and change in waist circumference after intervention in the obese group, and a significant positive correlation between the change in waist circumference and adiponectin and IGFBP-1 in the lean group.

Given the variations in intervention response observed between lean and obese children, the investigators concluded that exercise and lifestyle interventions should be different in these subgroups of children, with obese children requiring more intensive intervention with specifically modified diet, Dr. Purushothaman reported.

The data also suggest that improvement in biochemical parameters can occur even before changes in BMI, and they may be associated with a decrease in body fat percentage, Dr. Purushothaman stated.

She noted that longer term follow-up is needed to determine if the metabolic changes are sustainable and whether obese children will start showing improvement with longer periods of intervention.

In terms of the larger groups, there was no difference at baseline across the three groups in BMI, percentage body fat, waist circumference, lipid profile, adiponectin, acute insulin response, IGF-BP-1, QUICKI, and glucose disposition index, Dr. Purushothaman reported.

After 12 weeks, the glucose disposition index improved significantly in both intervention groups. The lifestyle plus exercise intervention was associated with increases in acute insulin response and BMI and decreases in body fat, while both intervention groups showed decreases in adiponectin and IGFBP-1. ■

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to 100 mg/kg/day (approximately 11 times the maximum recommended human oral dose based on mg/m^2). No drug-induced tumors were observed in any organ.

During prospective evaluation of urinary cytology involving more than 1800 patients receiving ACTOS in clinical trials up to one year in duration, no new cases of bladder tumors were identified. In two 3-year studies in which pioglitazone was compared to placebo or glyburide, there were 16/3656 (0.44%) reports of bladder cancer in patients taking pioglitazone compared to 5/3679 (0.14%) in patients not taking pioglitazone. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were six (0.16%) cases on pioglitazone and two (0.05%) on placebo.

Pioglitazone HCl was not mutagenic in a battery of genetic toxicology studies, including the Ames bacterial assay, a mammalian cell forward gene mutation assay (CHO/HPRT and AS52/XPRT), an *in vitro* cytogenetics assay using CHL cells, an unscheduled DNA synthesis assay, and an *in vivo* micronucleus assay.

No adverse effects upon fertility were observed in male and female rats at oral doses up to 40 mg/kg pioglitazone HCl daily prior to and throughout mating and gestation (approximately 9 times the maximum recommended human oral dose based on mg/m^2).

Animal Toxicology
Heart enlargement has been observed in mice (100 mg/kg), rats (4 mg/kg and above) and dogs (3 mg/kg) treated orally with pioglitazone HCl (approximately 11, 1, and 2 times the maximum recommended human oral dose for mice, rats, and dogs, respectively, based on mg/m^2). In a one-year rat study, drug-related early death due to apparent heart dysfunction occurred at an oral dose of 160 mg/kg/day (approximately 35 times the maximum recommended human oral dose based on mg/m^2). Heart enlargement was seen in a 13-week study in monkeys at oral doses of 8.9 mg/kg and above (approximately 4 times the maximum recommended human oral dose based on mg/m^2), but not in a 52-week study at oral doses up to 32 mg/kg (approximately 13 times the maximum recommended human oral dose based on mg/m^2).

Pregnancy
Pregnancy Category C. Pioglitazone was not teratogenic in rats at oral doses up to 80 mg/kg or in rabbits given up to 160 mg/kg during organogenesis (approximately 17 and 40 times the maximum recommended human oral dose based on mg/m^2, respectively). Delayed parturition and embryotoxicity (as evidenced by increased postimplantation losses, delayed development and reduced fetal weights) were observed in rats at oral doses of 40 mg/kg/day and above (approximately 10 times the maximum recommended human oral dose based on mg/m^2). No functional or behavioral toxicity was observed in offspring of rats. In rabbits, embryotoxicity was observed at an oral dose of 160 mg/kg (approximately 40 times the maximum recommended human oral dose based on mg/m^2). Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats at oral doses of 10 mg/kg and above during late gestation and lactation periods (approximately 2 times the maximum recommended human oral dose based on mg/m^2).

There are no adequate and well-controlled studies in pregnant women. ACTOS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies, as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers
Pioglitazone is secreted in the milk of lactating rats. It is not known whether ACTOS is secreted in human milk. Because many drugs are excreted in human milk, ACTOS should not be administered to a breastfeeding woman.

Pediatric Use
Safety and effectiveness of ACTOS in pediatric patients have not been established.

Elderly Use
Approximately 500 patients in placebo-controlled clinical trials of ACTOS were 65 and over. No significant differences in effectiveness and safety were observed between these patients and younger patients.

ADVERSE REACTIONS
Over 8500 patients with type 2 diabetes have been treated with ACTOS in randomized, double-blind, controlled clinical trials. This includes 2605 high-risk patients with type 2 diabetes treated with ACTOS from the PROactive clinical trial. Over 6000 patients have been treated for 6 months or longer, and over 4500 patients for one year or longer. Over 3000 patients have received ACTOS for at least 2 years.

The overall incidence and types of adverse events reported in placebo-controlled clinical trials of ACTOS monotherapy at doses of 7.5 mg, 15 mg, 30 mg, or 45 mg once daily are shown in Table 2.

Table 2 Placebo-Controlled Clinical Studies of ACTOS Monotherapy: Adverse Events Reported at a Frequency ≥ 5% of Patients Treated with ACTOS

(% of Patients)		
	Placebo N=259	ACTOS N=606
Upper Respiratory Tract Infection	8.5	13.2
Headache	6.9	9.1
Sinusitis	4.6	6.3
Myalgia	2.7	5.4
Tooth Disorder	2.3	5.3
Diabetes Mellitus Aggravated	8.1	5.1
Pharyngitis	0.8	5.1

For most clinical adverse events the incidence was similar for groups treated with ACTOS monotherapy and those treated in combination with sulfonylureas, metformin, and insulin. There was an increase in the occurrence of edema in the patients treated with ACTOS and insulin compared to insulin alone.

In a 16-week, placebo-controlled ACTOS plus insulin trial (n=379), 10 patients treated with ACTOS plus insulin developed dyspnea and also, at some point during their therapy, developed either weight change or edema. Seven of these 10 patients received diuretics to treat these symptoms. This was not reported in the insulin plus placebo group.

The incidence of withdrawals from placebo-controlled clinical trials due to an adverse event other than hyperglycemia was similar for patients treated with placebo (2.8%) or ACTOS (3.3%).

In controlled combination therapy studies with either a sulfonylurea or insulin, mild to moderate hypoglycemia, which appears to be dose related, was reported (see **PRECAUTIONS**, **General**, Hypoglycemia).

In U.S. double-blind studies, anemia was reported in ≤ 2% of patients treated with ACTOS plus sulfonylurea, metformin or insulin (see **PRECAUTIONS**, **General**, Hematologic).

In monotherapy studies, edema was reported for 4.8% (with doses from 7.5 mg to 45 mg) of patients treated with ACTOS versus 1.2% of placebo-treated patients. In combination therapy studies, edema was reported for 7.2% of patients treated with ACTOS and sulfonylureas compared to 2.1% of patients on sulfonylureas alone. In combination therapy studies with metformin, edema was reported in 6.0% of patients on combination therapy compared to 2.5% of patients on metformin alone. In combination therapy studies with insulin, edema was reported in 15.3% of patients on combination therapy compared to 7.0% of patients on insulin alone. Most of these events were considered mild or moderate in intensity (see **PRECAUTIONS**, **General**, Edema).

In one 16-week clinical trial of insulin plus ACTOS combination therapy, more patients developed congestive heart failure on combination therapy (1.1%) compared to none on insulin alone (see **WARNINGS**, **Cardiac Failure and Other Cardiac Effects**).

Prospective Pioglitazone Clinical Trial In Macrovascular Events (PROactive)
In PROactive, 5238 patients with type 2 diabetes and a prior history of macrovascular disease were treated with ACTOS (n=2605), force-titrated up to 45 mg daily or placebo (n=2633) in addition to standard of care. Almost all subjects (95%) were receiving cardiovascular medications (beta blockers, ACE inhibitors, ARBs, calcium channel blockers, nitrates, diuretics, aspirin, statins, fibrates). Patients had a mean age of 61.8 years, mean duration of diabetes 9.5 years, and mean HbA_{1c} 8.1%. Average duration of follow-up was 34.5 months. The primary objective of this trial was to examine the effect of ACTOS on mortality and macrovascular morbidity in patients with type 2 diabetes mellitus who were at high risk for macrovascular events. The primary efficacy variable was the time to the first occurrence of any event in the cardiovascular composite endpoint (see **Table 3** below). Although there was no statistically significant difference between ACTOS and placebo for the 3-year incidence of a first event within this composite, there was no increase in mortality or in total macrovascular events with ACTOS.

Table 3

Number of First and Total Events for Each Component within the Cardiovascular Composite Endpoint				
	Placebo N=2633		ACTOS N=2605	
Cardiovascular Events	First Events (N)	Total Events (N)	First Events (N)	Total Events (N)
Any event	572	900	514	803
All-cause mortality	122	186	110	177
Non-fatal MI	118	157	105	131
Stroke	96	119	76	92
ACS	63	78	42	65
Cardiac intervention	101	240	101	195
Major leg amputation	15	28	9	28
Leg revascularization	57	92	71	115

Postmarketing reports of new onset or worsening diabetic macular edema with decreased visual acuity have also been received (see **PRECAUTIONS, General,** Macular Edema).

Laboratory Abnormalities
Hematologic: ACTOS may cause decreases in hemoglobin and hematocrit. The fall in hemoglobin and hematocrit with ACTOS appears to be dose related. Across all clinical studies, mean hemoglobin values declined by 2% to 4% in patients treated with ACTOS. These changes generally occurred within the first 4 to 12 weeks of therapy and remained relatively stable thereafter. These changes may be related to increased plasma volume associated with ACTOS therapy and have rarely been associated with any significant hematologic clinical effects.

Serum Transaminase Levels: During all clinical studies in the U.S., 14 of 4780 (0.30%) patients treated with ACTOS had ALT values ≥ 3 times the upper limit of normal during treatment. All patients with follow-up values had reversible elevations in ALT. In the population of patients treated with ACTOS, mean values for bilirubin, AST, ALT, alkaline phosphatase, and GGT were decreased at the final visit compared with baseline. Fewer than 0.9% of patients treated with ACTOS were withdrawn from clinical trials in the U.S. due to abnormal liver function tests.

In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure (see **PRECAUTIONS**, **General**, Hepatic Effects).

CPK Levels: During required laboratory testing in clinical trials, sporadic, transient elevations in creatine phosphokinase levels (CPK) were observed. An isolated elevation to greater than 10 times the upper limit of normal was noted in 9 patients (values of 2150 to 11400 IU/L). Six of these patients continued to receive ACTOS, two patients had completed receiving study medication at the time of the elevated value and one patient discontinued study medication due to the elevation. These elevations resolved without any apparent clinical sequelae. The relationship of these events to ACTOS therapy is unknown.

OVERDOSAGE
During controlled clinical trials, one case of overdose with ACTOS was reported. A male patient took 120 mg per day for four days, then 180 mg per day for seven days. The patient denied any clinical symptoms during this period.

In the event of overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

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