Stimulant May Affect Adolescents' CV Systems

BY ROBERT FINN

HONOLULU — High-dose OROS methylphenidate was associated with small but statistically significant increases in systolic blood pressure and heart rate in a 6-month, open-label study in adolescents.

The study found that there were no significant long-term increases in diastolic blood pressure or in electrocardiographic measures, Dr. Paul Hammerness said at the annual meeting of the American Academy of Child and Adolescent Psychiatry.

The findings are consistent with other studies involving younger children and lower doses, said Dr. Hammerness of Massachusetts General Hospital and Harvard Medical School, Boston. Because of concerns about possible associations between stimulant medications for attention-deficit/hyperactivity disorder (ADHD) and cardiovascular complications—including sudden cardiac death—the Food and Drug Administration recommended in June 2009 that physicians pay special attention to a child's cardiovascular system when prescribing stimulants.

The study involved 114 adolescents with a mean age of 14 years at baseline (range, 12 to 18 years). All of the subjects were healthy, and all had a diagnosis of ADHD based on full DSM-IV criteria. The trial was intended to evaluate the use of OROS methylphenidate for the prevention of cigarette smoking (J. Pediatr. 2009;155:84-9).

VITALS

Major Findings: Patients' mean heart rate increased significantly from 82 beats per minute at baseline to around 86 beats per minute at week 6 and at 6 months of using the OROS methylphenidate.

Source of Data: An open-label trial of 114 adolescents with ADHD.

Disclosures: The study was sponsored by McNeil, which markets OROS methylphenidate under the brand name Concerta. Dr. Hammerness acknowledged serving as a speaker for, receiving research funds from, or participating in CME activities or professional talks supported by several pharmaceutical companies, including McNeil.

Participants were excluded if they had a history of cardiovascular disease or had untreated mood or anxiety disorders, eating disorders, psychosis, or substance use disorders. Participants who were on stable regimens of benzodiazepines or antidepressants (other than monoamine oxidase inhibitors) could be admitted into the study.

The beginning dose of OROS methylphenidate was 0.5-0.75 mg/kg per day, and that was titrated to a maximum of 1.5 mg/kg per day by week 3. At week 6, the mean total daily dose was 63 mg, and 50% of the participants were taking 72 mg or more.

As expected, OROS methylphenidate was highly effective in treating the participants' ADHD. Their Rating Scale scores declined from a mean of 26.9 at baseline to 9.7 at week 6.

Of the 114 participants who entered the study, 73% were male, and their mean body mass index was 22.6 kg/m^2. At the time of data analysis, 57 participants had completed 6 months of treatment.

Mean systolic blood pressure at baseline was 113 mm Hg, and that increased to 117 mm Hg at 6 months, a significant increase. Mean diastolic blood pressure began at 63 mm Hg, increased significantly to 65 mm Hg at week 6, but then returned to 64 mm Hg at 6 months. Mean heart rate began at 82 beats per minute, increased significantly to 86 beats per minute at week 6, and remained at about that rate at 6 months.

The investigators found no statistically significant or clinically meaningful changes in ECG variables, including PR, QRS, or QTC.

Reasoning that any adverse cardiovascular effects of OROS methylphenidate might be restricted to certain subsets of adolescents, the investigators separately analyzed those 16 participants who met criteria for pre-hypertension or hypertension at baseline, based on at least one blood pressure reading above the 90th or 95th percentile. The investigators found no impact of abnormal premedication blood pressure readings on blood pressure changes during treatment.

None of the participants experienced serious adverse events or serious cardiovascular adverse events during the study. Ten of the 114 subjects reported one or more subjective cardiovascular complaints, including palpitations, chest pain, and fast or racing heartbeat. Of those, six had a lifetime diagnosis of comorbid anxiety disorder.

One participant discontinued treatment because of recurrent palpitations. She had a lifetime history of comorbid generalized anxiety disorder and migraines. But she showed no change from baseline in any cardiovascular measurement, and her primary care physician did not find her complaints to be consistent with cardiac disease. She later used a different stimulant medication with no subsequent cardiovascular symptoms.

"The FDA continues to review and still concludes that the overall risk-benefit ratio supports the use of stimulant medications for ADHD," Dr. Hammerness said. But he did recommend that clinicians carefully evaluate a child's cardiovascular symptoms and family history before prescribing stimulants. ■

CBT Alone Effective in ADHD/Substance Abuse Trial

BY BETSY BATES

LOS ANGELES — Psychostimulant treatment did not outperform placebo when structured cognitive-behavioral therapy was integrated into the treatment of adolescents with attention-deficit/hyperactivity disorder and substance use disorders.

In a 16-week, randomized, placebo-controlled trial, ADHD symptoms significantly improved and substance use declined regardless of whether adolescents received OROS-MPH (Concerta) or placebo, Dr. Paula Riggs said at the annual meeting of the American Academy of Addiction Psychiatry.

Rather than being seen as a negative trial, the study appears to speak to the usefulness of structured, individualized weekly CBT, said Dr. Riggs, the primary investigator of the 11-center trial sponsored by the National Institute of Drug Abuse and professor of psychiatry at the University of Colorado, Denver.

The trial enrolled 303 adolescents aged 13-18 who met DSM-IV criteria for ADHD and for at least substance use disorder (other than nicotine dependence, and excluding current opiate dependence or methamphetamine abuse or dependence).

The average age of participants was 16.5 years. About 80% of the participants were male, and 20% female. Whites constituted 64% of the medication arm and 55% of the placebo arm. Roughly a fourth of the subjects in each group were African American; 15% were Hispanic.

About one-third of subjects had ADHD-inattentive type; 67% had ADHD-combined type; and less than 2%, ADHD-hyperactive type.

Cannabis and alcohol use/dependence were the most commonly represented substance use disorders, although use and/or abuse of hallucinogens, opioids, cocaine, and amphetamines also were reported.

Adolescents with major depression, anxiety disorders, and/or conduct disorder were included in the trial, resulting in a high baseline level of psychopathology among participants. Almost 75% of the subjects completed the trial.

VITALS

Major finding: ADHD symptoms improved and substance use declined with CBT, regardless of whether adolescents received OROS-MPH or placebo.

Source of data: A randomized controlled trial with 303 adolescents with ADHD and a substance use disorder.

Disclosures: The trial was sponsored by the National Institute of Drug Abuse. The lead investigator reported no conflicts of interest.

"We wanted to keep this real and generalizable," Dr. Riggs said.

In the medication arm, 80% of 151 patients were compliant with doses, which were successfully titrated to 72 mg/daily in 96% and sustained at that dose in 86%.

Participants received either the active (titrated) drug or placebo along with weekly, individual CBT using a standardized manual targeting drug abuse.

An intent-to-treat analysis was used to calculate results.

"This was the shocker," Dr. Riggs said. "We saw a clinically and statistically significant reduction in ADHD symptoms in both groups."

Symptoms declined 46% in the medication group and 45% in the placebo group.

Parents reported symptom reductions of 26% and 30% in adolescents receiving active medication or placebo on a DSM-IV symptom checklist at 8 weeks, and 24% and 30.9% reductions at 16 weeks.

Past 28-day substance use reports declined by 6.1 days (43%) in the medication arm and 4.9 days (33%) in the placebo arm—a statistically insignificant between-group difference.

Slightly more negative drug screens—3.8 compared with 2.8—were found in adolescents assigned to receive active medication, and this group also showed greater improvements in problem-solving skills and focused-coping skills that had been addressed in CBT, Dr. Riggs reported.

Subjects deemed by investigators to be "medication responders" had twice as many negative drug screens as nonresponders or those receiving placebo.

Titrated OROS-MPH was "stunningly safe and well-tolerated" in the trial, with 11 serious adverse events, 7 of which occurred in the placebo group. The only event seen more frequently in the medication arm was limb injury, an event not considered to be related to the medication.

The trial results were inconsistent with the results of trials pitting psychostimulants against placebo in non–substance-abusing youth.

However, they were consistent with three previous controlled psychostimulant trials in non–substance-abusing adolescents when concurrent CBT was included for subjects in both the medication and placebo arms.

As in this trial, significant reductions were seen in ADHD in both groups, but with no significant advantage to medication over placebo. ■