

Fatty Liver Disease Common in U.S. Adolescents

BY MITCHEL L. ZOLER
Philadelphia Bureau

NEW ORLEANS — The prevalence of nonalcoholic fatty liver disease among U.S. children aged 9-19 years may be about 17%, far higher than previous estimates, based on an autopsy study of livers from 238 children from the San Diego area.

Among obese children aged 9-19, the prevalence of nonalcoholic fatty liver disease (NAFLD) was 45%, Jeffrey B.

Schwimmer, M.D., reported in a poster at the annual Digestive Disease Week.

With an estimated 9 million obese children in the United States today, "that's a lot of kids walking around with liver disease that no one knows about," said Dr. Schwimmer, a pediatrician and director of the fatty liver clinic at Children's Hospital and Health Center, San Diego. "Liver disease is the most common serious complication of obesity in children."

Until now, overall prevalence estimates

for NAFLD in children have ranged from about 2% to 8%. To get a more definitive handle on the scope of the problem, Dr. Schwimmer and his associates reviewed liver biopsies taken from children aged 2-19 who died suddenly in San Diego County during January 2000-July 2003. Causes of death included accidents, homicides, and suicides. The decedents' racial makeup was 42% white, 36% Hispanic, 9% African American, 8% Asian, and 4% other. The weight breakdown was 5% underweight (defined as 15th percentile or lower), 58% normal weight (16th-84th percentile), 14% overweight (85th-94th percentile), and 24% obese (95th percentile or higher).

The liver biopsies were read by a hepatopathologist who was blinded to the study. NAFLD was defined as macrovesicular steatosis involving at least 5% of hepatocytes. Decedents were excluded from analysis if their necropsy was done more than 48 hours after time of death.

NAFLD was not found in any child younger than 9 years. Of the 278 children aged 9-19 with necropsy studies, 238 had liver biopsies available for review. The average age of the children in this group was 17 years, and 180 (75.6%) were boys.

NAFLD was 3.3-fold more common in boys than in girls in an adjusted analysis, and prevalence increased with age. In children aged 9-15, the prevalence was about 10%, but it rose to 18% in those aged 17-19 years. NAFLD was most common in Hispanics (22%), followed by whites (15%), African Americans (8%), and Asians (5%). The higher rate in Hispanics persisted even when rates were also adjusted for obesity and other confounders, indicating that race and ethnicity has an independent role in the development of fatty liver disease.

When stratified by weight, the prevalence of NAFLD liver disease was 8% in the underweight kids, 7% in those with normal weight, 18% in the overweight children, and 45% in the obese children.

Diagnosing NAFLD in children in everyday practice can be a challenge for physicians. In a separate talk at the meeting, Dr. Schwimmer and his associates presented their findings from 100 children, 2-18 years old, who presented to his clinic during 1997-2003 with biopsy-proven NAFLD.

"Most of the children were asymptomatic; about a third had vague abdominal pain," he said.

A careful physical examination can reveal hepatomegaly in most children with NAFLD, but palpating the liver in an obese child can be difficult. Another physical flag is a tender edge on the liver, but again, detecting this requires experience and a thorough examination.

Most children with NAFLD will have an abnormally high level of at least one liver enzyme—alanine aminotransferase, aspartate aminotransferase, or gamma glutamyltransferase. But physicians have to be careful about what their laboratory is flagging as above normal for these enzymes. Because NAFLD is so common, upper limits of normal have crept up, Dr. Schwimmer said. Some laboratories are calling an ALT level of 75 U/L normal, which can be the level in children with cirrhosis. "Anything above 40 U/L is likely a marker of disease," he said.

Another flag for NAFLD in obese children is acanthosis nigricans.

The 100-patient series also showed that the form of nonalcoholic steatohepatitis (NASH) that often appears in liver biopsies of children with NAFLD is distinct from the type of NASH that is typical in adults. Adult-type NASH, named type 1 by Dr. Schwimmer and his associates, is a steatosis with ballooning degeneration and/or perisinusoidal fibrosis with or without lobular inflammation and without portal inflammation or fibrosis.

Pediatric-type NASH, named type 2, features steatosis with portal inflammation and/or fibrosis without perisinusoidal fibrosis or lobular inflammation.

In the 100 patients reviewed, type 2 NASH was seen in 41 patients, and type 1 was found in 12. All of the biopsies from the seven patients studied who had advanced liver fibrosis or cirrhosis had type 2 disease. Type 2 NASH was also associated with male gender, greater adiposity, and nonwhite race, which may explain why the histologic findings in pediatric NASH often differed from adult NASH. The differences between types 1 and 2 may correlate with differences in pathogenesis, natural history, and treatment response, Dr. Schwimmer said.

BRIEF SUMMARY

For Intravenous Infusion Only
DESCRIPTION

Adenosine is an endogenous nucleoside occurring in all cells of the body. It is chemically 6-amino-9-beta-D-ribofuranosyl-9-H-purine. Adenosine is a white crystalline powder. It is soluble in water and practically insoluble in alcohol. Solubility increases by warming and lowering the pH of the solution.

Each Adenoscan vial contains a sterile, non-pyrogenic solution of adenosine 3 mg/mL and sodium chloride 9 mg/mL. In Water for Injection, q.s. The pH of the solution is between 4.5 and 7.5.

INDICATIONS AND USAGE:
Intravenous Adenoscan is indicated as an adjunct to thallium-201 myocardial perfusion scintigraphy in patients unable to exercise adequately. (See **WARNINGS**.)

CONTRAINDICATIONS:
Intravenous Adenoscan should not be administered to individuals with:
1. Second- or third-degree AV block (except in patients with a functioning artificial pacemaker).
2. Sinus node disease, such as sick sinus syndrome or symptomatic bradycardia (except in patients with a functioning artificial pacemaker).
3. Known or suspected bronchoconstrictive or bronchospastic lung disease (e.g., asthma).
4. Known hypersensitivity to adenosine.

WARNINGS:
Fatal Cardiac Arrest, Life-Threatening Ventricular Arrhythmias, and Myocardial Infarction.
Fatal cardiac arrest, sustained ventricular tachycardia (requiring resuscitation), and nonfatal myocardial infarction have been reported coincident with Adenoscan infusion. Patients with unstable angina may be at greater risk. Appropriate resuscitative measures should be available.

Sinusal and Atrioventricular Nodal Block
Adenoscan exerts a direct depressant effect on the SA and AV nodes and has the potential to cause first-, second- or third-degree AV block, or sinus bradycardia. Approximately 6.3% of patients develop AV block with Adenoscan, including first-degree (2.9%), second-degree (2.6%) and third-degree (0.8%) heart block. All episodes of AV block have been asymptomatic, transient, and did not require intervention. Adenoscan can cause sinus bradycardia. Adenoscan should be used with caution in patients with pre-existing first-degree AV block or bundle branch block and should be avoided in patients with high-grade AV block or sinus node dysfunction (except in patients with a functioning artificial pacemaker). Adenoscan should be discontinued in any patient who develops persistent or symptomatic high-grade AV block. Sinus pause has been rarely observed with adenosine infusions.

Hypotension
Adenoscan is a potent peripheral vasodilator and can cause significant hypotension. Patients with an intact baroreceptor reflex mechanism are able to maintain blood pressure and tissue perfusion in response to Adenoscan by increasing heart rate and cardiac output. However, Adenoscan should be used with caution in patients with autonomic dysfunction, stenotic valvular heart disease, pericarditis or pericardial effusions, stenotic carotid artery disease with cerebrovascular insufficiency, or uncorrected hypovolemia, due to the risk of hypotensive complications in these patients. Adenoscan should be discontinued in any patient who develops persistent or symptomatic hypotension.

Hypertension
Increases in systolic and diastolic pressure have been observed (as great as 140 mm Hg systolic in one case) concomitant with Adenoscan infusion; most increases resolved spontaneously within several minutes, but in some cases, hypertension lasted for several hours.

Bronchoconstriction
Adenoscan is a respiratory stimulant (probably through activation of carotid body chemoreceptors) and intravenous administration in man has been shown to increase minute ventilation (V_E) and reduce arterial P_{CO2}, causing respiratory alkalosis. Approximately 28% of patients experience breathlessness (dyspnea) or an urge to breathe deeply with Adenoscan. These respiratory complaints are transient and only rarely require intervention.

Adenoscan administered by inhalation has been reported to cause bronchoconstriction in asthmatic patients, presumably due to mast cell degranulation and histamine release. This effect has not been observed in normal subjects. Adenoscan has been administered to a limited number of patients with asthma and mild to moderate exacerbation of their symptoms has been reported. Respiratory compromise has occurred during adenosine infusion in patients with obstructive pulmonary disease. Adenoscan should be used with caution in patients with obstructive lung disease not associated with bronchoconstriction (e.g., emphysema, bronchitis, etc.) and should be avoided in patients with bronchoconstriction or bronchospasm (e.g., asthma). Adenoscan should be discontinued in any patient who develops severe respiratory difficulties.

PRECAUTIONS:
Drug Interactions
Intravenous Adenoscan has been given with other cardioactive drugs (such as beta adrenergic blocking agents, cardiac glycosides, and calcium channel blockers) without adverse interactions, but its effectiveness with these agents has not been systematically evaluated. Because of the potential for additive or synergistic depressant effects on the SA and AV nodes, however, Adenoscan should be used with caution in the presence of these agents. The vasoactive effects of Adenoscan are inhibited by adenosine receptor antagonists, such as methylxanthines (e.g., caffeine and theophylline). The safety and efficacy of Adenoscan in the presence of these agents has not been systematically evaluated. The vasoactive effects of Adenoscan are potentiated by nucleoside transport inhibitors, such as dipyridamole. The safety and efficacy of Adenoscan in the presence of dipyridamole has not been systematically evaluated. Whenever possible, drugs that might inhibit or augment the effects of Adenoscan should be withheld for at least five half-lives prior to the use of Adenoscan.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Studies in animals have not been performed to evaluate the carcinogenic potential of Adenoscan. Adenoscan was negative for genotoxic potential in the Salmella (Ames Test) and Mammalian Microsome Assay. Adenosine, however, like other nucleosides at millimolar concentrations present for several doubling times of cells in culture, is known to produce a variety of chromosomal alterations. Fertility studies in animals have not been conducted with adenosine.

Pregnancy Category C
Animal reproduction studies have not been conducted with adenosine; nor have studies been performed in pregnant women. Because it is not known whether Adenoscan can cause fetal harm when administered to pregnant women, Adenoscan should be used during pregnancy only if clearly needed.

Pediatric Use
The safety and effectiveness of Adenoscan in patients less than 18 years of age has not been established.

Geriatric Use
Clinical studies of Adenoscan did not include sufficient numbers of subjects aged younger than 65 years to determine whether they respond differently. Other reported experience has not revealed clinically relevant differences of the response of elderly in comparison to younger patients. Greater sensitivity of some older individuals, however, cannot be ruled out.

ADVERSE REACTIONS:
The following reactions with an incidence of at least 1% were reported with intravenous Adenoscan among 1421 patients enrolled in controlled and uncontrolled U.S. clinical trials. Despite the short half-life of adenosine, 10.6% of the side effects occurred not with the infusion of Adenoscan but several hours after the infusion terminated. Also, 8.4% of the side effects that began coincident with the infusion persisted for up to 24 hours after the infusion was complete. In many cases, it is not possible to know whether these late adverse events are the result of Adenoscan infusion.

Flushing	44%	Lightheadedness/dizziness	12%	Hypotension	2%
Chest discomfort	40%	Upper extremity discomfort	4%	Nervousness	2%
Dyspnea or urge to breathe deeply	25%	ST segment depression	3%	Arrhythmias	1%
Headache	18%	First-degree AV block	3%		
Throat, neck or jaw discomfort	15%	Second-degree AV block	3%		
Gastrointestinal discomfort	13%	Parosmia	2%		

Adverse experiences of any severity reported in less than 1% of patients include:
Body as a Whole: back discomfort; lower extremity discomfort; weakness.
Cardiovascular System: nonfatal myocardial infarction; life-threatening ventricular arrhythmia; third-degree AV block; bradycardia; palpitation; sinus exit block; sinus pause; sweating; T-wave changes; hypertension (systolic blood pressure > 200 mm Hg).
Central Nervous System: drowsiness; emotional instability; tremors.
Genital/Urinary System: vaginal pressure; urgency.
Respiratory System: cough.
Special Senses: blurred vision; dry mouth; ear discomfort; metallic taste; nasal congestion; scotomas; tongue discomfort.

OVERDOSAGE:
The half-life of adenosine is less than 10 seconds and side effects of Adenoscan (when they occur) usually resolve quickly when the infusion is discontinued, although delayed or persistent effects have been observed. Methylxanthines, such as caffeine and theophylline, are competitive adenosine receptor antagonists and theophylline has been used to effectively terminate persistent side effects. In controlled U.S. clinical trials, theophylline (50-125 mg slow intravenous injection) was needed to abort Adenoscan side effects in less than 2% of patients.

DOSE AND ADMINISTRATION:
For intravenous infusion only.
Adenoscan should be given as a continuous peripheral intravenous infusion.
The recommended intravenous dose for adults is 140 mcg/kg/min infused for six minutes (total dose of 0.84 mg/kg).
The required dose of thallium-201 should be injected at the midpoint of the Adenoscan infusion (i.e., after the first three minutes of Adenoscan).
Thallium-201 is physically compatible with Adenoscan and may be injected directly into the Adenoscan infusion set.
The injection should be as close to the venous access as possible to prevent an inadvertent increase in the dose of Adenoscan (the contents of the IV tubing being administered). There are no data on the safety or efficacy of alternative Adenoscan infusion protocols.
The safety and efficacy of Adenoscan administered by the intracranial route have not been established.
Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.
Rx only
Fujisawa Healthcare, Inc.
Deerfield, IL 60015

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