Lab Values May Prove Useful in Appendicitis Dx

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SAN FRANCISCO — The diagnosis of appendicitis is notoriously difficult in children, with estimates of misdiagnosis rates ranging from 28% to 57% for children over the age of 12 and up to 100% for children under 2 years of age.

But the diagnosis may be made with high specificity using a combination of C-reactive protein and white blood cell levels, suggest the findings of a poster presented by Dr. Karen Y. Kwan and Dr. Alan L. Nager at the annual meeting of the Pediatric Academic Societies.

In particular, a C-reactive protein (CRP) level of 1.0 mg/dL or greater combined with a WBC count of 15,000 cells/mm^{3}or greater yields a specificity of 90%, a sensitivity of 49%, a positive predictive value of 86%, and a negative predictive value of 59% for confirmed appendicitis.

The study, conducted at the University of Southern California, Los Angeles, involved 209 patients aged 1-18 years presenting at a tertiary urban children's hospital with abdominal pain suspicious for acute appendicitis. In addition to history, physical exam, x-ray studies, and histopathology, the investigators conducted blood tests for CRP, WBC, D-lactate, and procalcitonin. Two to 6 weeks following discharge from the emergency department, investigators followed up with the patients to determine the ultimate diagnosis.

Of the 209 patients, 115 (55%) had confirmed appendicitis and 94 (45%) were negative. Among the diagnoses for children negative for appendicitis were constipation, gastroenteritis, pyelonephritis, ovarian torsion, and neoplasm.

The mean D-lactate values did not differ between patients who were positive and negative for appendicitis. The values of the other three lab markers did differ significantly; in each case patients with appendicitis had a significantly higher level than patients without.

Using a cutoff value of 1.0 mg/dL of CRP alone would yield a sensitivity of 84% and a specificity of 70%. A combination of that CRP cutoff with a WBC cutoff greater than 15,000 cells/mm^3 results in a somewhat lower sensitivity, a specificity of 90%, and the positive predictive value of 86%.

The investigators advised interpreting their findings with caution as 85% of the patients were Hispanic and largely indigent, and acute or chronic diseases may skew the laboratory values.

The meeting was sponsored by the American Pediatric Society, the Society for Pediatric Research, the Ambulatory Pediatric Association, and the American Academy of Pediatrics. ■

Once-daily
METADATE CD
(methylphenidate HCl, USP)
Extended-Release Capsules

℞ Only

BRIEF SUMMARY: Please see full Prescribing Information.

INDICATION AND USAGE: Attention Deficit Hyperactivity Disorder (ADHD): METADATE CD is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The efficacy of METADATE CD in the treatment of ADHD was established in one controlled trial of children aged 6 to 15 who met DSM-IV criteria for ADHD (see CLINICAL PHARMACOLOGY in full Prescribing Information).

CONTRAINDICATIONS: Agitation: METADATE CD is contraindicated in patients with marked anxiety, tension and agitation, since the drug may aggravate these symptoms.

Psychiatric History: METADATE CD should not be used in patients with severe depression, schizophrenic symptoms, psychopathological personality structure, history of aggression, or suicidal tendency.

Hypersensitivity to Methylphenidate: METADATE CD is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product.

Glaucoma: METADATE CD is contraindicated in patients with glaucoma.

Tics: METADATE CD is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome (see ADVERSE REACTIONS).

Monoamine Oxidase Inhibitors: METADATE CD is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of a monoamine oxidase inhibitor (hypertensive crises may result).

Hypertension and Other Cardiovascular Conditions: METADATE CD is contraindicated in patients with severe hypertension, angina pectoris, cardiac arrhythmias, heart failure, recent myocardial infarction, hyperthyroidism or thyrotoxicosis (see WARNINGS).

WARNINGS: Depression: METADATE CD should not be used to treat severe depression.

Fatigue: METADATE CD should not be used for the prevention or treatment of normal fatigue states.

Long-Term Suppression of Growth: Sufficient data on the safety of long-term use of methylphenidate in children are not yet available. Although a causal relationship has not been established, suppression of growth (i.e., weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored. Patients who are not growing or gaining weight as expected should have their treatment interrupted.

Psychosis: Clinical experience suggests that in psychotic patients, administration of methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder.

Seizures: There is some clinical evidence that methylphenidate may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Sudden Death and Pre-existing Structural Cardiac Abnormalities: Sudden death has been reported in association with CNS stimulant treatment at usual doses in children with structural cardiac abnormalities. Although some structural cardiac abnormalities alone may carry an increased risk of sudden death, stimulant products generally should not be used in children, adolescents, or adults with known structural cardiac abnormalities.

Hypertension and Other Cardiovascular Conditions: Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in patients taking METADATE CD, especially patients with hypertension. Studies of methylphenidate have shown modest increases of resting pulse and systolic and diastolic blood pressure. Therefore, caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension (see CONTRAINDICATIONS).

Visual Disturbance: Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

Use in Children Under Six Years of Age: METADATE CD should not be used in children under six years, since safety and efficacy in this age group have not been established.

DRUG DEPENDENCE: METADATE CD should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

PRECAUTIONS: Hematologic Monitoring: Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Information for Patients: Patients should be instructed to take one dose in the morning before breakfast. The patients should be instructed that the capsule may be swallowed whole, or alternatively, the capsule may be opened and the capsule contents sprinkled onto a small amount (tablespoon) of applesauce and given immediately, and not stored for future use. The capsules and the capsule contents must not be crushed or chewed.

To assure safe and effective use of METADATE CD, the information and instructions provided in the patient information section should be discussed with patients.

Drug Interactions: Because of possible effects on blood pressure, METADATE CD should be used cautiously with pressor agents.

Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). Downward dose adjustment of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing concomitant methylphenidate.

Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 4 times the maximum recommended human dose of METADATE CD on a mg/kg and mg/m^2 basis, respectively. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 22 times and 5 times the maximum recommended human dose of METADATE CD on a mg/kg and mg/m^2 basis, respectively.

In a 24-week carcinogenicity study in the transgenic mouse strain p53+/-, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60 to 74 mg/kg/day of methylphenidate.

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay in cultured Chinese Hamster Ovary cells. Methylphenidate was negative *in vivo* in males and females in the mouse bone marrow micronucleus assay.

Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately 80-fold and 8-fold the highest recommended human dose of METADATE CD on a mg/kg and mg/m^2 basis, respectively.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day, which is approximately 100 times and 40 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively.

A reproduction study in rats revealed no evidence of teratogenicity at an oral dose of 58 mg/kg/day. However, this dose, which caused some maternal toxicity, resulted in decreased postnatal pup weights and survival when given to the dams from day one of gestation through the lactation period. This dose is approximately 30 fold and 6 fold the maximum recommended human dose of METADATE CD on a mg/kg and mg/m^2 basis, respectively.

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

Nursing Mothers: It is not known whether methylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if METADATE CD is administered to a nursing woman.

Pediatric Use: The safety and efficacy of METADATE CD in children under 6 years old have not been established. Long-term effects of methylphenidate in children have not been well established (see WARNINGS).

ADVERSE REACTIONS: The premarketing development program for METADATE CD included exposures in a total of 228 participants in clinical trials (188 pediatric patients with ADHD, 40 healthy adult subjects). These participants received METADATE CD 20, 40, and/or 60 mg/day. The 188 patients (ages 6 to 15) were evaluated in one controlled clinical study, one controlled, crossover clinical study, and one uncontrolled clinical study. Safety data on all patients are included in the discussion that follows. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings in Clinical Trials with METADATE CD: Adverse Events Associated with Discontinuation of Treatment: In the 3-week placebo-controlled, parallel-group trial, two METADATE CD-treated patients (1%) and no placebo-treated patients discontinued due to an adverse event (rash and pruritus; and headache, abdominal pain, and dizziness, respectively).

Adverse Events Occurring at an Incidence of 5% or more Among METADATE CD-Treated Patients: Table 1 enumerates, for a pool of the three studies in pediatric patients with ADHD, at METADATE CD doses of 20, 40, or 60 mg/day, the incidence of treatment-emergent adverse events. One study was a 3-week placebo-controlled, parallel-group trial, one study was a controlled, crossover trial, and the third was an open titration trial. The table includes only those events that occurred in 5% or more of patients treated with METADATE CD where the incidence in patients treated with METADATE CD was greater than the incidence in placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

TABLE 1
Incidence of Treatment-Emergent Events[1] in a Pool of 3-4 Week Clinical Trials of METADATE CD

Body System	Preferred Term	METADATE CD (n=188)	Placebo (n=190)
General	Headache	12%	8%
	Abdominal pain (stomach ache)	7%	4%
Digestive System	Anorexia (loss of appetite)	9%	2%
Nervous System	Insomnia	5%	2%

[1]: Events, regardless of causality, for which the incidence for patients treated with METADATE CD was at least 5% and greater than the incidence among placebo-treated patients. Incidence has been rounded to the nearest whole number.

Adverse Events with Other Marketed Methylphenidate HCl Products: Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. There have been rare reports of Tourette's Syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: instances of abnormal liver function, ranging from transaminase elevation to hepatic coma; isolated cases of cerebral arteritis and/or occlusion; leucopenia and/or anemia; transient depressed mood; a few instances of scalp hair loss. Very rare reports of neuroleptic malignant syndrome (NMS) have been reported, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten year old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

Postmarketing Experience: In addition to the adverse events listed above, the following have been reported in patients receiving METADATE CD worldwide. The list is alphabetized: abnormal behavior, aggression, anxiety, cardiac arrest, depression, fixed drug eruption, hyperactivity, irritability, sudden death, suicidal behavior (including completed suicide), and thrombocytopenia. Data are insufficient to support an estimation of incidence or establish causation.

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: METADATE CD, like other methylphenidate products, is classified as a Schedule II controlled substance by federal regulation.

Abuse, Dependence, and Tolerance: See WARNINGS for boxed warning containing drug abuse and dependence information.

OVERDOSAGE: Signs and Symptoms: Signs and symptoms of acute methylphenidate overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Recommended Treatment: Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage as indicated. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal hemodialysis for METADATE CD overdosage has not been established.

The prolonged release of methylphenidate from METADATE CD should be considered when treating patients with overdose.

Poison Control Center: As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of overdosage with methylphenidate.

FOR MEDICAL INFORMATION
Contact: Medical Affairs Department
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Fax: (770) 970-8859

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Hand Cleansers' Push Bars Are Germ Hangouts

LISBON — The dispensers of alcohol-based disinfectant for hand washing that are ubiquitous in hospitals and physicians' offices are often contaminated with bacteria, including potential pathogens, Dr. Kiran Mangalpally cautioned at the 12th International Congress on Infectious Diseases.

He cultured the push bars of 44 such dispensers at Mount Vernon (N.Y.) Hospital, where he is a resident in internal medicine. Thirty-five, or 80%, proved culture positive.

The push bars are activated by pressure applied by the palm or fingers, which releases a squirt of hand rinse or foam. But the disinfectant does not reach the push bar itself. Twenty-nine of the push bars grew coagulase-negative staphylococci and four grew *Staphylococcus aureus*, including two that yielded methicillin-resistant *S. aureus*. Another two push bars grew nonstaphylococcal bacteria.

For comparison, Dr. Mangalpally also cultured 11 doorknobs from hospital bathrooms. Nine of the 11 proved culture positive, all of which grew only coagulase-negative staphylococci. "This is one of those simple things we don't think about much," he noted in an interview at the congress sponsored by the International Society for Infectious Diseases.

An alternative to push bar–operated dispensers are touch-free dispensers operated by foot pump, electronic sensor, or voice activation technology. These devices are commercially available from major manufacturers, he noted.

—Bruce Jancin