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Watch for Foodborne Illness

The recent *Escherichia coli* outbreak in Germany reminds us yet again about the threat of foodborne illness and the need for awareness about the clinical manifestations, the treatment, and the public health implications. On June 14, a 2-year-old boy became the first child and the 37th person to die in Germany's ongoing *E. coli* outbreak. Here in the United States, the Centers for Disease Control and Prevention estimates 48 million people – 1 in every 6 Americans – become ill, 128,000 are hospitalized, and 3,000 die of foodborne illness annually. About half of all foodborne illness occurs in children, who are particularly vulnerable because of their immature immune systems, lower body weight, and reduced stomach acid production.

Norovirus has become the most common recognized foodborne pathogen, causing about 5 million illnesses a year, followed by nontyphoidal *Salmonella*, with just over 1 million annual cases, and *Clostridium perfringens*, at just under 1 million, according to the CDC. *Norovirus* illness is usually mild, but it did cause an estimated 149 annual deaths. Nontyphoidal *Salmonella* is the most common serious cause of foodborne illness with an estimated 378 annual deaths, followed by *Toxoplasma gondii* (327 deaths) and *Listeria monocytogenes* (255 deaths).

The following foodborne illnesses are frequent causes of morbidity in children.

Information on the possible foodborne sources and the effects of infection are from a report compiled by the Pew Health Group in collaboration with the Center for Foodborne Illness Research and Prevention.

► ***Salmonella.*** These infections occur in approximately 75 children/100,000 under age 4 years, according to the CDC. It is commonly associated with foods of animal origin, including beef, poultry, milk, and eggs, or cross-contamination from these with other foods. Typical symptoms include diarrhea, fever, and abdominal cramps. More serious short-term manifestations can include colitis, meningitis, septicemia, and death. Treatment involves rehydration as needed.

In general, antibiotic therapy is not warranted, but in immunocompromised hosts and children younger than age 6 months, antimicrobial therapy may be beneficial. In such settings, ceftriaxone is effective when susceptible, specifically in high-risk populations.

► ***Shigella.*** This infection occurs in about 28/100,000 children under age 4 years and 26/100,000 for those aged 4-11 years, according to the CDC. It is often associated with vegetables harvested in fields contaminated with sewage; flies that breed in infected feces and contaminate the food; and drinking, swimming, or playing in contaminated water. Short-term effects include high fever, diarrhea that is often bloody, stomach cramps, and seizures in children less than age 2 years. Reactive or chronic arthritis can be a postinfectious sequelae.

Treatment includes rehydration as necessary, and antibiotics for severe disease or dysentery, particularly in those with underlying immunosuppression. Ceftriaxone and ciprofloxacin are effective, although the latter is not licensed for use in young children. Resistance to amoxicillin and trimethoprim-sulfamethoxazole (TMP-SMZ) is common. Treatment of mild cases may be indicated to shorten the duration of excretion.

► ***Campylobacter.*** This infection affects 29/100,000 children under age 4 years, similar in incidence to *Shigella*. Foodborne sources included raw or undercooked poultry or foods cross-contaminated by poultry, unpasteurized milk, and contaminated water. Symptoms include diarrhea (sometimes bloody), cramping, abdominal pain, urinary tract infection, fever, and meningitis. *Campylobacter* is also associated with Guillain-Barré syndrome or reactive/chronic arthritis. Again, treatment involves rehydration as necessary. Macrolides (azithromycin or erythromycin) can shorten duration of illness and prevent relapse.

► ***E. coli* or other shiga toxin–producing strains.** This foodborne infection has been in the headlines lately, and affects about 4/100,000 children between 4 and 11 years of age. Typical food sources include ground beef and other meats, green leafy vegetables, unpasteurized juices or raw milk, or soft cheeses made from raw milk. Symptoms include severe stomach cramps, diarrhea (often bloody), and vomiting. Hemolytic-uremic syndrome occurs in about 15% of children with *E. coli* 0157:H7 infection. This can result in long-term kidney damage as well as death.

In general, antibiotics have not been shown to benefit patients. Early reports of increased risk of hemolytic-uremic syndrome with antibiotic treatment have not been confirmed. As with the others, rehydration and supportive therapy are the mainstays of treatment.

► ***Listeria.*** This infection occurs in about 0.76/100,000 children under age 4 years, according to the CDC. About one-third of all cases involve pregnant women. Common food sources include uncooked meats, particularly cold cuts and hot dogs, as well as smoked seafood, raw milk, soft cheeses made from raw milk, and vegetables grown in contaminated soil or fertilizer. Symptoms include fever, muscle aches, nausea, and diarrhea. Headaches, stiff neck, confusion, loss of balance, and seizures can result if infection spreads to the nervous system.

For invasive disease, ampicillin plus an aminoglycoside is recommended. For penicillin-allergic patients, TMP-SMZ or high-dose vancomycin can be used. Cephalosporins are generally inactive. In the majority of patients with febrile gastroenteritis, the illness is self-limited (typical duration, 2 days or less) and therefore, generally no antibiotic treatment is necessary.

In pregnant women, listerial febrile gastroenteritis can lead to fetal death, premature birth, or infected newborns. Oral ampicillin or TMP-SMZ can be given for several days in immunocompromised or pregnant patients with listerial febrile gastroenteritis, particularly if they are still symptomatic once the culture result is known. ■

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Table 4 Common Adverse Reactions in the Flexible-Dose Adjunctive to Stimulant Therapy Trial- Treatment Period (Study 2)

Preferred Term	Percentage of Patients Reporting Event	
	KAPVAY+STM (N=102)	PBO+STM (N=96)
Somnolence[1]	19%	8%
Fatigue[2]	16%	4%
Abdominal Pain Upper	12%	7%
Nasal Congestion	6%	5%
Throat Pain	6%	3%
Decreased Appetite	5%	4%
Body Temperature Increased	4%	2%
Dizziness	4%	2%
Insomnia	4%	2%
Epistaxis	3%	0
Rhinorrhea	3%	0
Abdominal Pain	2%	1%
Anxiety	2%	0
Pain in Extremity	2%	0

1. Somnolence includes the terms: "somnolence" and "sedation".

2. Fatigue includes the terms "fatigue" and "lethargy".

Commonly observed adverse reactions (incidence of ≥ 2% in the treatment group and greater than the rate on placebo) during the taper period are listed in Table 5.

Table 5 Common Adverse Reactions in the Flexible-Dose Adjunctive to Stimulant Therapy Trial- Taper Period* (Study 2)

Preferred Term	Percentage of Patients Reporting Event	
	KAPVAY+STM (N=102)	PBO+STM (N=96)
Nasal Congestion	4%	2%
Headache	3%	1%
Irritability	3%	2%
Throat Pain	3%	1%
Gastroenteritis Viral	2%	0
Rash	2%	0

*Taper Period: weeks 6-8.

Most common adverse reactions, defined as events that were reported in at least 5% of drug-treated patients and at least twice the rate as in placebo patients, during the treatment period were somnolence, fatigue, upper respiratory tract infection, irritability, throat pain, insomnia, nightmares, emotional disorder, constipation, nasal congestion, increased body temperature, dry mouth, and ear pain. The most common adverse reactions that were reported during the taper phase were upper abdominal pain and gastrointestinal virus.

Adverse Reactions Leading to Discontinuation

Thirteen percent (13%) of patients receiving KAPVAY discontinued from the pediatric monotherapy study due to adverse events, compared to 1% in the placebo group. The most common adverse reactions leading to discontinuation of KAPVAY monotherapy treated patients were from somnolence/sedation (5%) and fatigue (4%). Less common adverse reactions leading to discontinuation (occurring in approximately 1% of patients) included: formication, vomiting, prolonged QT, increased heart rate, and rash. In the pediatric adjunctive treatment to stimulants study, one patient discontinued from KAPVAY + stimulant group because of bradyphrenia.

Effects on Laboratory Tests, Vital Signs, and Electrocardiograms

KAPVAY treatment was not associated with any clinically important effects on any laboratory parameters in either of the placebo-controlled studies.

Mean decreases in blood pressure and heart rate were seen [see Warnings and Precautions (5.1)].

There were no changes on ECGs to suggest a drug-related effect.

DRUG INTERACTIONS

No drug interaction studies have been conducted with KAPVAY in children. The following have been reported with other oral immediate release formulations of clonidine.

Interactions with CNS-depressant Drugs

Clonidine may potentiate the CNS-depressive effects of alcohol, barbiturates or other sedating drugs.

Interactions with Tricyclic Antidepressants

If a patient is receiving clonidine hydrochloride and also taking tricyclic antidepressants the hypotensive effects of clonidine may be reduced.

Interactions with Drugs Known to Affect Sinus Node Function or AV Nodal Conduction

Due to a potential for additive effects such as bradycardia and AV block, caution is warranted in patients receiving clonidine concomitantly with agents known to affect sinus node function or AV nodal conduction (e.g., digitalis, calcium channel blockers and beta-blockers).

Use with other products containing clonidine

Do not use KAPVAY concomitantly with other products containing clonidine (e.g. Catapres®).

Antihypertensive Drugs

Use caution when KAPVAY is administered concomitantly with antihypertensive drugs, due to the potential for additive pharmacodynamic effects (e.g., hypotension, syncope) [*see Warnings and Precautions (5.2)*].

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C: Oral administration of clonidine hydrochloride to pregnant rabbits during the period of embryo/fetal organogenesis at doses of up to 80 mcg/kg/day (approximately 3 times the oral maximum recommended daily dose [MRHD] of 0.4 mg/day on a mg/m^2 basis) produced no evidence of teratogenic or embryotoxic potential. In pregnant rats, however, doses as low as 15 mcg/kg/day (1/3 the MRHD on a mg/m^2 basis) were associated with increased resorptions in a study in which dams were treated continuously from 2 months prior to mating and throughout gestation. Increased resorptions were not associated with treatment at the same or at higher dose levels (up to 3 times the MRHD) when treatment of the dams was restricted to gestation days 6-15. Increases in resorptions were observed in both rats and mice at 500 mcg/kg/day (10 and 5 times the MRHD in rats and mice, respectively) or higher when the animals were treated on gestation days 1-14; 500 mcg/kg/day was the lowest dose employed in this study. No adequate and well-controlled studies have been conducted in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should not be used during pregnancy unless clearly needed.

Nursing Mothers

Since clonidine hydrochloride is excreted in human milk, caution should be exercised when KAPVAY is administered to a nursing woman.

Pediatric Use

A study was conducted in which young rats were treated orally with clonidine hydrochloride from day 21 of age to adulthood at doses of up to 300 mcg/kg/day, which is approximately 3 times the maximum recommended human dose (MRHD) of 0.4 mg/day on a mg/m^2 basis. A slight delay in onset of preputial separation was seen in males treated with the highest dose (with a no-effect dose of 100 mcg/kg/day, which is approximately equal to the MRHD), but there were no drug effects on fertility or on other measures of sexual or neurobehavioral development.

KAPVAY has not been studied in children with ADHD less than 6 years old.

Patients with Renal Impairment

The impact of renal impairment on the pharmacokinetics of clonidine in children has not been assessed. The initial dosage of KAPVAY should be based on degree of impairment. Monitor patients carefully for hypotension and bradycardia, and titrate to higher doses cautiously. Since only a minimal amount of clonidine is removed during routine hemodialysis, there is no need to give supplemental KAPVAY following dialysis.

Adult Use in ADHD

KAPVAY has not been studied in adult patients with ADHD.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

KAPVAY is not a controlled substance and has no known potential for abuse or dependence.

OVERDOSAGE

Symptoms

Clonidine overdose: hypertension may develop early and may be followed by hypotension, bradycardia, respiratory depression, hypothermia, drowsiness, decreased or absent reflexes, weakness, irritability and miosis. The frequency of CNS depression may be higher in children than adults. Large overdoses may result in reversible cardiac conduction defects or dysrhythmias, apnea, coma and seizures. Signs and symptoms of overdose generally occur within 30 minutes to two hours after exposure.

Treatment

Consult with a Certified Poison Control Center for up-to-date guidance and advice.

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