AAP Endorses New Rabies Vaccine Schedule

BY SHARON WORCESTER

FROM PEDIATRICS

The American Academy of Pediatrics has officially endorsed a 2010 recommendation by the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices that reduces by one the number of vaccine doses required for postexposure rabies prophylaxis.

The recommendation calls for reduction in the number of post-exposure doses of human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV) from five to four doses, with the first dose of 1 mL to be given intramuscularly as soon as possible after exposure (day 0) and subsequent doses to be given on days 3, 7, and 14 after the first dose except in people with immune suppression, who should continue to receive the five-dose regimen with the fifth dose given on day 28.

The recommendation is the result of a review beginning in 2007 during a time when human rabies vaccine was in limited supply. The Advisory Committee on Immunization Practices (ACIP) formed a work group to review rabies vaccine options, and found that four doses were adequate for inducing rabies-neutralizing antibody, according to an AAP Policy Statement published in Pediatrics, which announced the AAP's endorsement of the recommendation (Pediatrics 2011 March 28 [doi: 10.1542/peds.2011-0095]).

A detailed review by the ACIP rabies work group of the evidence in support of the reduced dosing schedule showed that in all of approximately 1,000 patients, an adequate immune response

to vaccination was achieved by day 14 (when the fourth dose of cell-derived rabies vaccine was given).

In addition, observational studies of people with likely rabies exposure showed that no cases of rabies have been attributed to the lack of a fifth dose.

Furthermore, animal models demonstrated that the number of vaccine doses did not contribute to significant differences in survival rate, and, theoretically, a reduced dosing schedule would result in similar or reduced rates of adverse reactions, which already are uncommon in children even when five doses are given.

Finally, the ACIP recommendation, which was published in 2010 (MMWR 2010;59[RR-2]:1-9), showed that reducing the dosing schedule to four doses would result in an estimated $16.6 million cost savings to the U.S. health care system.

Approximately 20,000-30,000 people receive rabies postexposure prophylaxis (PEP) in the United States each year, and one to three cases of human rabies occur each year, according to the AAP Policy Statement. Since the 1970s, with the introduction of modern cell-derived vaccines, no PEP failures have occurred.

Effective PEP has been attributed to prompt washing of the wound with copious amounts of soap and water, infiltration of human rabies immunoglobulin (HRIG) into and around the wound, and an appropriate dose schedule of intramuscular vaccine, which is now considered to be four doses in most patients, according to the Policy Statement. All other rabies PEP recommendations remain the same.

It is important that pediatricians be up to date on the new recommendations for rabies PEP, Dr. Mary Ann Jackson said in an interview.

"Despite the rarity of human rabies infection in the United States, questions for the pediatrician arising from potential animal exposures are surprisingly frequent, as animal bites and even bat exposures occur not uncommonly in the pediatric population," said Dr. Jackson, chief of the pediatric infectious diseases section at Children's Mercy Hospitals & Clinics, Kansas City, Mo.

Pediatricians also need to know that the decision to embark on rabies PEP should be urgently but not emergently handled, she added, explaining that most exposures relate to domestic animal encounters (often strays) or incidents in which bats are found in the family home. "Careful attention to information gathering related to the exposure is key (see our form at www.childrensmercy.org/rabiesform), and practitioners should utilize their health department and local infectious disease specialists for input in situations where PEP is considered," she said.

Dr. Jackson, who also is a professor of pediatrics at the University of Missouri–Kansas City, advised that in any instance where PEP is being considered, it is important to keep in mind that wound cleansing is essential and the child's tetanus vaccine history should be confirmed, with vaccine provided in appropriate cases. Rabies immune globulin must be concurrently given in the wound site in addition to rabies vaccine in an alternative site in every case where PEP is being provided for the first time in an otherwise healthy child.

In the instance where a bat is discovered in the room of a sleeping child, the PEP decision is certainly straightforward if the animal is available for rabies testing, and results can be ascertained promptly. In an otherwise healthy domestic pet exposure, a 10-day observation period should be ensured, utilizing the assistance of the local animal control and public health officials and in low-risk situations, which may obviate the need for PEP, said Dr. Jackson, who is a member of the AAP Committee on Infectious Diseases that wrote the new AAP Policy Statement.

All authors have filed conflict of interest statements with the AAP. Any conflicts have been resolved through a process approved by the AAP Board of Directors, according to Pediatrics. ■

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/m² 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/m² 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/m² 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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