

Mother's Vitamin D Supplement May Benefit Infant

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CHARLESTON, S.C. — Give breast-feeding women enough vitamin D and you may supplement their babies, too, according to the results of a small but promising pilot study presented at a pediatric meeting sponsored by the Medical University of South Carolina.

"Our question was: 'Would direct vitamin D supplementation meet the needs of

both the mother and her nursing infant?'" said Dr. Carol L. Wagner of the department of neonatology at the university, in Charleston.

Insufficient vitamin D causes many problems, primarily a lack of calcium absorption that can lead to bone loss. In addition, recent research suggests a link between insufficient vitamin D and immune system disorders such as diabetes, Dr. Wagner said.

People in the developed world are at

risk for vitamin D deficiency because of a primarily indoor lifestyle that has limited adequate vitamin D intake from sunlight, she added.

Data from several recent studies suggest that doses of vitamin D that are significantly higher than the current recommended daily allowance will not cause toxicity and are in fact needed for adequate circulating 25-hydroxyvitamin D concentrations (25[OH]D).

To determine whether giving mothers

high doses of vitamin D provides adequate 25(OH)D for both mothers and infants without toxicity to either, Dr. Wagner and colleagues randomized 18 breast-feeding women to receive 400 IU or 6,400 IU of vitamin D₃ as a daily pill for 6 months starting at 1 month post partum.

The mothers who were randomized to 6,400 IU of vitamin D₃ showed a substantial increase in circulating calcium levels with no adverse effects.

In addition, compliance rates were more than 90% because the mothers said that they were more likely to remember to take a pill themselves than to give supplements to their babies.

The infants whose mothers took 400 IU received their own supplement of 300 IU daily, while the infants whose mothers took 6,400 IU received a placebo supplement.

"What we found was a wonderful increase," in infant 25(OH)D levels from breast milk alone, Dr. Wagner said.

After 6 months, the average 25(OH)D level was 47 ng/mL in the mothers who received 6,400 IU and 46 ng/mL in their babies. By comparison, the average 25(OH)D level was 38 ng/mL in the mothers who received 400 IU and 43 ng/mL in their babies.

There were no adverse events in either mother or infant related to vitamin D toxicity.

"Supplementing the mom with high-dose vitamin D is still considered unproven," Dr. Wagner said. "We think it is safe, but we have to study it in large numbers." A study of 389 lactating women at sites in Charleston, S.C., and Rochester, N.Y., is planned, and the researchers will assess factors including bone mineral density and immune function.

For now, Dr. Wagner encourages physicians to recommend vitamin D supplementation for breast-feeding infants, but if the circulating vitamin D levels in the mothers are 50 ng/mL or higher, the infants are probably getting enough, too. Strive for circulating 25(OH)D levels of at least 30 ng/mL in all patients, she emphasized.

The American Academy of Pediatrics currently recommends vitamin D supplementation for all breast-fed infants because mother's milk is generally deficient in vitamin D. But 25% of the vitamin D in lactating women goes into breast milk, and it seems that increasing vitamin D in mothers results in adequate vitamin D for the breast-fed infant, Dr. Wagner explained.

Because a mother is the only source of vitamin D for her developing fetus and the primary source for a breast-feeding infant, more research is needed on whether increasing maternal vitamin D will help infants, too.

Famvir® (famciclovir)

Tablets

Rx only

BRIEF SUMMARY: Please see package insert for full prescribing information.

INDICATIONS AND USAGE

Herpes Zoster: Famvir® (famciclovir) is indicated for the treatment of acute herpes zoster (shingles).

Herpes Simplex Infections: Famvir is indicated for:

- treatment or suppression of recurrent genital herpes in immunocompetent patients.
- treatment of recurrent herpes labialis (cold sores) in immunocompetent patients.
- treatment of recurrent mucocutaneous herpes simplex infections in HIV-infected patients.

CONTRAINDICATIONS

Famvir® (famciclovir) is contraindicated in patients with known hypersensitivity to the product, its components, and Denavir® (penciclovir cream).

PRECAUTIONS

General

The efficacy of Famvir® (famciclovir) has not been established for initial episode genital herpes infection, ophthalmic zoster, disseminated zoster or in immunocompromised patients with herpes zoster.

Dosage adjustment is recommended when administering Famvir to patients with creatinine clearance values <60 mL/min. (See **DOSAGE AND ADMINISTRATION** in the full prescribing information). In patients with underlying renal disease who have received inappropriately high doses of Famvir for their level of renal function, acute renal failure has been reported.

Famvir 125 mg, 250 mg and 500 mg tablets contain lactose (26.9 mg, 53.7 mg and 107.4 mg, respectively). Patients with rare hereditary problems of galactose intolerance, a severe lactase deficiency or glucose-galactose malabsorption should not take Famvir 125 mg, 250 mg and 500 mg tablets.

Information for Patients

Patients should be informed that Famvir is not a cure for genital herpes. There are no data evaluating whether Famvir will prevent transmission of infection to others. As genital herpes is a sexually transmitted disease, patients should avoid contact with lesions or intercourse when lesions and/or symptoms are present to avoid infecting partners. Genital herpes can also be transmitted in the absence of symptoms through asymptomatic viral shedding. If medical management of recurrent episodes is indicated, patients should be advised to initiate therapy at the first sign or symptom.

There is no evidence that Famvir will affect the ability of a patient to drive or to use machines. However, patients who experience dizziness, somnolence, confusion or other central nervous system disturbances while taking Famvir should refrain from driving or operating machinery.

Drug Interactions

Concurrent use with probenecid or other drugs significantly eliminated by active renal tubular secretion may result in increased plasma concentrations of penciclovir.

The conversion of 6-deoxy penciclovir to penciclovir is catalyzed by aldehyde oxidase. Interactions with other drugs metabolized by this enzyme could potentially occur.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Famciclovir was administered orally unless otherwise stated.

Carcinogenesis: Two-year dietary carcinogenicity studies with famciclovir were conducted in rats and mice. An increase in the incidence of mammary adenocarcinoma (a common tumor in animals of this strain) was seen in female rats receiving the high dose of 600 mg/kg/day (1.1 to 4.5x the human systemic exposure at the recommended total daily oral dose ranging between 2000 mg and 500 mg, based on area under the plasma concentration curve comparisons [24 hr AUC] for penciclovir). No increases in tumor incidence were reported in male rats treated at doses up to 240 mg/kg/day (0.7 to 2.7x the human AUC), or in male and female mice at doses up to 600 mg/kg/day (0.3 to 1.2x the human AUC).

Mutagenesis: Famciclovir and penciclovir (the active metabolite of famciclovir) were tested for genotoxic potential in a battery of *in vitro* and *in vivo* assays. Famciclovir and penciclovir were negative in *in vitro* tests for gene mutations in bacteria (*S. typhimurium* and *E. coli*) and unscheduled DNA synthesis in mammalian HeLa 83 cells (at doses up to 10,000 and 5,000 mcg/plate, respectively). Famciclovir was also negative in the L5178Y mouse lymphoma assay (5000 mcg/mL), the *in vivo* mouse micronucleus test (4800 mg/kg), and rat dominant lethal study (5000 mg/kg). Famciclovir induced increases in polyploidy in human lymphocytes *in vitro* in the absence of chromosomal damage (1200 mcg/mL). Penciclovir was positive in the L5178Y mouse lymphoma assay for gene mutation/chromosomal aberrations, with and without metabolic activation (1000 mcg/mL). In human lymphocytes, penciclovir caused chromosomal aberrations in the absence of metabolic activation (250 mcg/mL). Penciclovir caused an increased incidence of micronuclei in mouse bone marrow *in vivo* when administered intravenously at doses highly toxic to bone marrow (500 mg/kg), but not when administered orally.

Impairment of Fertility: Testicular toxicity was observed in rats, mice, and dogs following repeated administration of famciclovir or penciclovir. Testicular changes included atrophy of the seminiferous tubules, reduction in sperm count, and/or increased incidence of sperm with abnormal morphology or reduced motility. The degree of toxicity to male reproduction was related to dose and duration of exposure. In male rats, decreased fertility was observed after 10 weeks of dosing at 500 mg/kg/day (1.4 to 5.7x the human AUC). The no observable effect level for sperm and testicular toxicity in rats following chronic administration (26 weeks) was 50 mg/kg/day (0.15 to 0.6x the human systemic exposure based on AUC comparisons). Testicular toxicity was observed following chronic administration to mice (104 weeks) and dogs (26 weeks) at doses of 600 mg/kg/day (0.3 to 1.2x the human AUC) and 150 mg/kg/day (1.3 to 5.1x the human AUC), respectively.

Famciclovir had no effect on general reproductive performance or fertility in female rats at doses up to 1000 mg/kg/day (2.7 to 10.8x the human AUC).

Two placebo-controlled studies in a total of 130 otherwise healthy men with a normal sperm profile over an 8-week baseline period and recurrent genital herpes receiving oral Famvir (250 mg b.i.d.) (n=66) or placebo (n=64) therapy for 18 weeks showed no evidence of significant effects on sperm count, motility or morphology during treatment or during an 8 week follow-up.

Pregnancy

Teratogenic Effects—Pregnancy Category B: Famciclovir was tested for effects on embryo-fetal development in rats and rabbits at oral doses up to 1000 mg/kg/day (approximately 2.7 to 10.8x and 1.4 to 5.4x the human systemic exposure to penciclovir based on AUC comparisons for the rat and rabbit, respectively) and intravenous doses of 360 mg/kg/day in rats (1.5 to 6x the human dose based on body surface area [BSA] comparisons) or 120 mg/kg/day in rabbits (1.1 to 4.5x the human dose [BSA]). No adverse effects were observed on embryo-fetal development. Similarly, no adverse effects were observed following intravenous administration of penciclovir to rats (80 mg/kg/day, 0.3 to 1.3x the human dose [BSA]) or rabbits (60 mg/kg/day, 0.5 to 2.1x the human dose [BSA]). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, famciclovir should be used during pregnancy only if the benefit to the patient clearly exceeds the potential risk to the fetus.

Pregnancy Exposure Registry: To monitor maternal-fetal outcomes of pregnant women exposed to Famvir, Novartis Pharmaceuticals Corporation maintains a Famvir Pregnancy Registry. Physicians are encouraged to register their patients by calling (888) 669-6662.

Nursing Mothers

Following oral administration of famciclovir to lactating rats, penciclovir was excreted in breast milk at concentrations higher than those seen in the plasma. It is not known whether it is excreted in human milk. There are no data on the safety of Famvir in infants.

Usage in Children

Safety and efficacy in children under the age of 18 years have not been established.

Geriatric Use

Of 816 patients with herpes zoster in clinical studies who were treated with Famvir, 248 (30.4%) were ≥65 years of age and 103 (13%) were ≥75 years of age. No overall differences were observed in the incidence or types of adverse events between younger and older patients.

Of 610 patients with recurrent herpes simplex (type 1 or type 2) in clinical studies who were treated with Famvir, 26 (4.3%) were ≥65 years of age and 7 (1.1%) were ≥75 years of age. Clinical studies of Famvir did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

In general, appropriate caution should be exercised in the administration and monitoring of FAMVIR in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Immunocompetent Patients

The safety of Famvir® (famciclovir) has been evaluated in clinical studies involving 816 Famvir-treated patients with herpes zoster (Famvir, 250 mg t.i.d. to 750 mg t.i.d.); 163 Famvir-treated patients with recurrent genital herpes (Famvir, 1000 mg b.i.d.); 1,197 patients with recurrent genital herpes treated with Famvir as suppressive therapy (125 mg q.d. to 250 mg t.i.d.) of which 570 patients received Famvir (open-labeled and/or double-blind) for at least 10 months; and 447 Famvir-treated patients with herpes labialis (Famvir, 1500 mg once or 750 mg b.i.d.). Table 5 lists selected adverse events.

Table 5
Selected Adverse Events (all grades and without regard to causality) Reported by
≥2% of Patients in Placebo-controlled Famvir® (famciclovir) Trials*

Event	Incidence							
	Herpes Zoster†		Recurrent Genital Herpes†		Genital Herpes-Suppression‡		Herpes Labialis‡	
	Famvir® 500 mg t.i.d.* (n=273) %	Placebo (n=146) %	Famvir® 1 gram b.i.d.* (n=163) %	Placebo (n=166) %	Famvir® 250 mg b.i.d.* (n=458) %	Placebo (n=63) %	Famvir® 1500 mg single dose* (n=227) %	Placebo (n=254) %
Nervous System								
Headache	22.7	17.8	13.5	5.4	39.3	42.9	9.7	6.7
Paresthesia	2.6	0.0	0.0	0.0	0.9	0.0	0.0	0.0
Migraine	0.7	0.7	0.6	0.6	3.1	0.0	0.0	0.0
Gastrointestinal								
Nausea	12.5	11.6	2.5	3.6	7.2	9.5	2.2	3.9
Diarrhea	7.7	4.8	4.9	1.2	9.0	9.5	1.8	0.8
Vomiting	4.8	3.4	1.2	0.6	3.1	1.6	0.0	0.0
Flatulence	1.5	0.7	0.6	0.0	4.8	1.6	0.0	0.0
Abdominal Pain	1.1	3.4	0.0	1.2	7.9	7.9	0.0	0.4
Body as a Whole								
Fatigue	4.4	3.4	0.6	0.0	4.8	3.2	1.3	0.4
Skin and Appendages								
Pruritus	3.7	2.7	0.0	0.6	2.2	0.0	0.0	0.0
Rash	0.4	0.7	0.0	0.0	3.3	1.6	0.0	0.0
Reproductive Female								
Dysmenorrhea	0.0	0.7	1.8	0.6	7.6	6.3	0.9	0.0

*Patients may have entered into more than one clinical trial.

†7 days of treatment

‡1 day of treatment

§daily treatment

The following adverse events have been reported during post-approval use of Famvir: urticaria, hallucinations and confusion (including delirium, disorientation, confusional state, occurring predominantly in the elderly). Because these adverse events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. Table 6 lists selected laboratory abnormalities in genital herpes suppression trials.

Table 6
Selected Laboratory Abnormalities in Genital Herpes Suppression Studies*

Parameter	Famvir® (n=660)† %	Placebo (n=210)† %
Anemia (<0.8 x NRL)	0.1	0.0
Leukopenia (<0.75 x NRL)	1.3	0.9
Neutropenia (<0.8 x NRL)	3.2	1.5
AST (SGOT) (>2 x NRH)	2.3	1.2
ALT (SGPT) (>2 x NRH)	3.2	1.5
Total Bilirubin (>1.5 x NRH)	1.9	1.2
Serum Creatinine (>1.5 x NRH)	0.2	0.3
Amylase (>1.5 x NRH)	1.5	1.9
Lipase (>1.5 x NRH)	4.9	4.7

*Percentage of patients with laboratory abnormalities that were increased or decreased from baseline and were outside of specified ranges.

†n values represent the minimum number of patients assessed for each laboratory parameter.

NRH = Normal Range High.

NRL = Normal Range Low.

HIV-Infected Patients

In HIV-infected patients, the most frequently reported adverse events for famciclovir (500 mg twice daily; n=150) and acyclovir (400 mg, 5x/day; n=143), respectively, were headache (16.7% vs. 15.4%), nausea (10.7% vs. 12.6%), diarrhea (6.7% vs. 10.5%), vomiting (4.7% vs. 3.5%), fatigue (4.0% vs. 2.1%), and abdominal pain (3.3% vs. 5.6%).

Post Marketing Experience

The following adverse events have been reported during post-approval use of Famvir: urticaria, serious skin reactions (e.g., erythema multiforme), jaundice, thrombocytopenia, hallucinations, dizziness, somnolence and confusion (including delirium, disorientation, confusional state, occurring predominantly in the elderly). Because these adverse events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]

REV: JULY 2006

Distributed by:
Novartis Pharmaceuticals Corp.
East Hanover, NJ 07936

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T2006-71