

Maternal Vitamin D Affects Children's Asthma Risk

BY PATRICE WENDLING
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MIAMI BEACH — High maternal vitamin D intake in pregnancy may help protect children from asthma and wheezing illnesses during early childhood, results of a large, prospective study suggest.

In multivariate analyses, every 100-IU increase in maternal vitamin D intake was associated with about a 10% lower risk for any wheeze (odds ratio 0.90) and with

nearly a 20% lower risk of having a child at high risk for asthma (OR 0.82). This inverse association was present whether vitamin D came from diet or nutritional supplements and remained after controlling for 10 confounding factors, Dr. Carlos A. Camargo Jr. reported at the annual meeting of the American Academy of Allergy, Asthma and Immunology.

"This is a new hypothesis, but the vitamin D story is going to be one that you're going to hear more and more about in the

years ahead," he told reporters at the meeting. "Already this year there is a lot of discussion going on about vitamin D and cancer. But to link this to asthma and allergic diseases is very exciting."

The best explanation for the observed protective effect is that vitamin D, which is known to have some immunologic effects, influences IL-10 secretion by regulatory T cells, said Dr. Camargo of the department of epidemiology at Harvard Medical School in Boston.

The findings suggest that vitamin D insufficiency is a reality, particularly in northern parts of the country. Exactly what the correct amount of daily vitamin D intake is remains unclear, in part because of emerging data from this and studies in other specialties, he said. "Most people in the field would recommend 800-1,000 IU/day, and yet you'll see recommendations of 200-400 IU in the literature," he said.

The mean vitamin D intake during pregnancy was 548 IU/day in the study, which included 1,194 mother-child pairs in Project Viva, a prospective prepartum co-

Van Kerrebroeck et al: A 12-week, double-blind, multicenter, randomized, placebo-controlled study to evaluate the efficacy and tolerability of tolterodine tartrate capsules (4 mg qd) compared with tolterodine tartrate tablets (2 mg bid) and placebo in 1529 patients with overactive bladder (published data from the Registration Study). The primary efficacy variable was the change in the number of incontinence episodes per week from baseline to Week 12.

Landis et al: A post hoc analysis of a 12-week, multinational, randomized, double-blind, placebo-controlled study that compared the efficacy of tolterodine tartrate capsules (4 mg qd) with placebo for overactive bladder in 986 patients with severe urgency incontinence. Severe urgency incontinence was defined as 21 to 168 urgency incontinence episodes/week.

References: 1. Van Kerrebroeck P, Kreder K, Jonas U, Zinner N, Wein A, for the Tolterodine Study Group. Tolterodine once-daily: superior efficacy and tolerability in the treatment of the overactive bladder. *Urology*. 2001;57:414-421. 2. Landis JR, Kaplan S, Swift S, Versi E. Efficacy of antimuscarinic therapy for overactive bladder with varying degrees of incontinence severity. *J Urol*. 2004;171:752-756.

Detrol LA[®]

tolterodine tartrate

extended release capsules

PHARMACIA

Brief Summary of Prescribing Information

INDICATIONS AND USAGE

DETROL LA Capsules are once daily extended release capsules indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

CONTRAINDICATIONS

DETROL LA Capsules are contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma. DETROL LA is also contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

PRECAUTIONS

General

Risk of Urinary Retention and Gastric Retention: DETROL LA Capsules should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention and to patients with gastrointestinal obstructive disorders, such as pyloric stenosis, because of the risk of gastric retention (see **CONTRAINDICATIONS**).

Controlled Narrow-Angle Glaucoma: DETROL LA should be used with caution in patients being treated for narrow-angle glaucoma.

Reduced Hepatic and Renal Function: For patients with significantly reduced hepatic function or renal function, the recommended dose for DETROL LA is 2 mg daily. (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations** in full prescribing information).

Patients with Congenital or Acquired QT Prolongation:

In a study of the effect of tolterodine immediate release tablets on the QT interval (See **CLINICAL PHARMACOLOGY, Cardiac Electrophysiology** in full prescribing information), the effect on the QT interval appeared greater for 8 mg/day (two times the therapeutic dose) compared to 4 mg/day and was more pronounced in CYP2D6 poor metabolizers (PMs) than extensive metabolizers (EMs). The effect of tolterodine 8 mg/day was not as large as that observed after four days of therapeutic dosing with the active control moxifloxacin. However, the confidence intervals overlapped. These observations should be considered in clinical decisions to prescribe DETROL LA for patients with a known history of QT prolongation or patients who are taking Class IA (eg, quinidine, procainamide) or Class III (eg, amiodarone, sotalol) antiarrhythmic medications (See **PRECAUTIONS, Drug Interactions**). There has been no association of Torsade de Pointes in the international post-marketing experience with DETROL or DETROL LA.

Information for Patients

Patients should be informed that antimuscarinic agents such as DETROL LA may produce the following effects: blurred vision, dizziness, or drowsiness.

Drug Interactions

CYP3A4 Inhibitors: Ketoconazole, an inhibitor of the drug metabolizing enzyme CYP3A4, significantly increased plasma concentrations of tolterodine when coadministered to subjects who were poor metabolizers (see **CLINICAL PHARMACOLOGY, Variability in Metabolism and Drug-Drug Interactions** in full prescribing information). For patients receiving ketoconazole or other potent CYP3A4 inhibitors such as other azole antifungals (eg, itraconazole, miconazole) or macrolide antibiotics (eg, erythromycin, clarithromycin) or cyclosporine or vinblastine, the recommended dose of DETROL LA is 2 mg daily (see **DOSAGE AND ADMINISTRATION**).

Drug-Laboratory-Test Interactions

Interactions between tolterodine and laboratory tests have not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with tolterodine immediate release were conducted in mice and rats. At the maximum tolerated dose in mice (30 mg/kg/day), female rats (20 mg/kg/day), and male rats (30 mg/kg/day), AUC values obtained for tolterodine were 355, 291, and 462 µg·h/L, respectively. In comparison, the human AUC value for a 2-mg dose administered twice daily is estimated at 34 µg·h/L. Thus, tolterodine exposure in the carcinogenicity studies was 9- to 14-fold higher than expected in humans. No increase in tumors was found in either mice or rats. No mutagenic effects of tolterodine were detected in a battery of in vitro tests, including bacterial mutation assays (Ames test) in 4 strains of *Salmonella typhimurium* and in 2 strains of *Escherichia coli*, a gene mutation assay in L5178Y mouse lymphoma cells, and chromosomal aberration tests in human lymphocytes. Tolterodine was also negative in vivo in the bone marrow micronucleus test in the mouse. In female mice treated for 2 weeks before mating and during gestation with 20 mg/kg/day (corresponding to AUC value of about 500 µg·h/L), neither effects on reproductive performance or fertility were seen. Based on AUC values, the systemic exposure was about 15-fold higher in animals than in humans. In male mice, a dose of 30 mg/kg/day did not induce any adverse effects on fertility.

Pregnancy

Pregnancy Category C. At oral doses of 20 mg/kg/day (approximately 14 times the human exposure), no anomalies or malformations were observed in mice. When given at doses of 30 to 40 mg/kg/day, tolterodine has been shown to be embryolethal and reduce fetal weight, and increase the incidence of fetal abnormalities (cleft palate, digital abnormalities, intra-abdominal hemorrhage, and various skeletal abnormalities, primarily reduced ossification) in mice. At these doses, the AUC values were about 20- to 25-fold higher than in humans. Rabbits treated subcutaneously at a dose of 0.8 mg/kg/day achieved an AUC of 100 µg·h/L, which is about 3-fold higher than that resulting from the human dose. This dose did not result in any embryotoxicity or teratogenicity. There are no studies of tolterodine in pregnant women. Therefore, DETROL LA should be used during pregnancy only if the potential benefit for the mother justifies the potential risk to the fetus.

Nursing Mothers

Tolterodine immediate release is excreted into the milk in mice. Offspring of female mice treated with tolterodine 20 mg/kg/day during the lactation period had slightly reduced bodyweight gain. The offspring regained the weight during the maturation phase. It is not known whether tolterodine is excreted in human milk; therefore, DETROL LA should not be administered during nursing. A decision should be made whether to discontinue nursing or to discontinue DETROL LA in nursing mothers.

Pediatric Use

Efficacy in the pediatric population has not been demonstrated. A total of 710 pediatric patients (486 on DETROL LA, 224 on placebo) aged 5-10 with urinary frequency and urge incontinence were studied in two Phase 3 randomized, placebo-controlled, double-blind, 12-week studies.

The percentage of patients with urinary tract infections was higher in patients treated with DETROL LA (6.6%) compared to patients who received placebo (4.5%). Aggressive, abnormal and hyperactive behavior and attention disorders occurred in 2.9% of children treated with DETROL LA compared to 0.9% of children treated with placebo.

Geriatric Use

No overall differences in safety were observed between the older and younger patients treated with tolterodine (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations** in full prescribing information).

ADVERSE REACTIONS

The Phase 2 and 3 clinical trial program for DETROL LA Capsules included 1073 patients who were treated with DETROL LA (n=537) or placebo (n=536). The patients were treated with 2, 4, 6, or 8 mg/day for up to 15 months. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates. The data described below reflect exposure to DETROL LA 4 mg once daily every morning in 505 patients and to placebo in 507 patients exposed for 12 weeks in the Phase 3, controlled clinical study.

Adverse events were reported in 52% (n=263) of patients receiving DETROL LA and in 49% (n=247) of patients receiving placebo. The most common adverse events reported by patients receiving DETROL LA were dry mouth, headache, constipation, and abdominal pain. Dry mouth was the most frequently reported adverse event for patients treated with DETROL LA occurring in 23.4% of patients treated with DETROL LA and 7.7% of placebo-treated patients. Dry mouth, constipation, abnormal vision (accommodation abnormalities), urinary retention, and dry eyes are expected side effects of antimuscarinic agents. A serious adverse event was reported by 1.4% (n=7) of patients receiving DETROL LA and by 3.6% (n=18) of patients receiving placebo.

The frequency of discontinuation due to adverse events was highest during the first 4 weeks of treatment. Similar percentages of patients treated with DETROL LA or placebo discontinued treatment due to adverse events. Treatment was discontinued due to adverse events and dry mouth was reported as an adverse event in 2.4% (n=12) of patients treated with DETROL LA and in 1.2% (n=6) of patients treated with placebo.

Table 4 lists the adverse events reported in 1% or more of patients treated with DETROL LA 4 mg once daily in the 12-week study. The adverse events were reported regardless of causality.

Table 4. Incidence* (% of Adverse Events Exceeding Placebo Rate and Reported in ≥1% of Patients Treated with DETROL LA (4 mg daily) in a 12-week, Phase 3 Clinical Trial

Body System	Adverse Event	% DETROL LA n=505	% Placebo n=507
Autonomic Nervous	dry mouth	23	8
	headache	6	4
General	fatigue	2	1
	dizziness	2	1
Central/Peripheral Nervous	constipation	6	4
	abdominal pain	4	2
	dyspepsia	3	1
Vision	xerophthalmia	3	2
	vision abnormal	1	0
Psychiatric	somnolence	3	2
	anxiety	1	0
Respiratory	sinusitis	2	1
	urinary	1	0

* in nearest integer.

Postmarketing Surveillance

The following events have been reported in association with tolterodine use in clinical practice: anaphylactoid reactions, including angioedema; tachycardia; palpitations; peripheral edema; and hallucinations. Because these spontaneously reported events are from the worldwide postmarketing experience, the frequency of events and the role of tolterodine in their causation cannot be reliably determined.

OVERDOSAGE

A 27-month-old child who ingested 5 to 7 tolterodine immediate release tablets 2 mg was treated with a suspension of activated charcoal and was hospitalized overnight with symptoms of dry mouth. The child fully recovered.

Management of Overdosage

Overdosage with DETROL LA Capsules can potentially result in severe central anticholinergic effects and should be treated accordingly. ECG monitoring is recommended in the event of overdosage. In dogs, changes in the QT interval (slight prolongation of 10% to 20%) were observed at a suprapharmacologic dose of 4.5 mg/kg, which is about 68 times higher than the recommended human dose. In clinical trials of normal volunteers and patients, QT interval prolongation was not observed with tolterodine immediate release at doses up to 8 mg (4 mg bid) and higher doses were not evaluated. (see **PRECAUTIONS, Patients with Congenital or Acquired QT Prolongation**).

DOSAGE AND ADMINISTRATION

The recommended dose of DETROL LA Capsules are 4 mg daily. DETROL LA should be taken once daily with liquids and swallowed whole. The dose may be lowered to 2 mg daily based on individual response and tolerability, however, limited efficacy data is available for DETROL LA 2 mg (see **CLINICAL STUDIES** in full prescribing information). For patients with significantly reduced hepatic or renal function or who are currently taking drugs that are potent inhibitors of CYP3A4, the recommended dose of DETROL LA is 2 mg daily (see **CLINICAL PHARMACOLOGY and PRECAUTIONS, Drug Interactions** in full prescribing information).

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DR. CAMARGO

hort study in Massachusetts. Intake was assessed using a validated food questionnaire in the first and second trimesters and was averaged for analyses.

Dr. Camargo and his colleagues defined any wheeze as a mother-reported wheeze or physician-diagnosed asthma, wheezing, or reactive airway disease at ages 1, 2, or 3 years. High risk of asthma was defined as the subset of children with two or more reports of wheezing at 1, 2, or 3 years, plus either parental history of asthma or child diagnosis of eczema. ■

Oxytocin May Prevent Placental Retention

MIAMI BEACH — Intraumbilical vein injection with oxytocin following cord clamp was effective for preventing placental retention and reducing postpartum blood loss in a randomized, placebo-controlled, double-blind study presented at the annual meeting of the Society for Maternal-Fetal Medicine.

The study is the first to suggest that oxytocin might be beneficial in preventing complications in the third stage of labor, though not its duration, said Dr. Labib M. Ghulmiyyah of the University of Cincinnati.

A total of 79 women with uncomplicated singleton pregnancies were randomized to 30 mL of saline or 20 IU of oxytocin in 30 mL of saline. The mean time to placental delivery did not differ significantly between the two groups, but significantly more women in the saline group than in the oxytocin group had a retained placenta after 15 minutes (5 vs. 0 women).

The groups had similar mean hemoglobin levels prior to delivery, but those who received saline had significantly lower mean postpartum hemoglobin levels (used as a measure of blood loss) than did those in the oxytocin group.

—Sharon Worcester

