

Oral Bacteria May Affect Pregnancy Outcome

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

The oral pathogen *Actinomyces naeslundii* appears to be associated with shorter gestation resulting in preterm low birth weight, while oral *Lactobacillus casei* is associated with longer gestation and higher birth weight.

Increased levels of *A. naeslundii* could account for as much as 4%-6% of preterm low-birth-weight babies, although more

research is necessary to confirm causality, said Ananda P. Dasanayake, D.D.S., of the New York University College of Dentistry, and his colleagues (J. Periodontol. 2005;76:171-7).

The epidemiologic study offers one more tantalizing glimpse at the interrelationship between oral health and systemic disease, and points up the importance of dental care during pregnancy.

"It is advisable to tell patients to seek dental care during pregnancy," Dr.

Dasanayake said in an interview. "If they have chronic periodontal disease, that can be treated—usually mechanically, by scaling and root planing, but sometimes with combination therapy that includes antibiotics."

Dr. Dasanayake and his colleagues compared the presence of oral bacteria during the third trimester and at delivery with pregnancy outcomes in 297 primigravidae. The women's mean age was 20 years; 93% were African American. About 85%

had at least a high school education. Saliva samples were obtained by expectoration after chewing on sterile paraffin wax.

Samples were tested for *A. naeslundii*, *L. casei*, *Streptococcus mutans*, *Streptococcus sobrinus*, *Streptococcus sanguinus*, and *Lactobacillus acidophilus*.

Most of the women (67%) had normal vaginal deliveries. The average infant birth weight was 3,200 g and average gestational age was 39 weeks. There were 26 low-birth-weight deliveries and 28 preterm deliveries.

In a multivariate analysis, the only bacteria significantly associated with pregnancy outcomes were *A. naeslundii* and *L. casei*.

Increasing numbers of *A. naeslundii* were significantly associated with preterm low birth weight.

For every one-unit increase in *A. naeslundii* levels, there was a 60-g decrease in birth weight and a 0.17-week decrease in gestational age.

L. casei was associated with increasing gestational age.

Each unit increase in *L. casei* was associated with a 0.13-week increase in gestational age.

The connection between oral bacteria and preterm birth is biologically plausible, Dr. Dasanayake said.

Increased levels of *A. naeslundii* could account for as much as 4%-6% of preterm low-birth-weight babies; more research is needed to confirm causality.

Infections trigger inflammation and increase cytokines, which in turn can increase prostaglandins and lead to cervical dilation and uterine contraction.

Conversely, oral *L. casei*—which is associated with the incidence of dental caries—can have a protective effect by colonizing the vagina (migrating via elimination), where it suppresses the growth of pathogenic bacteria and inhibits bacterial vaginosis.

Because of the epidemiologic nature of the study, he said, it was not possible to separate the actual effect of either bacterial level from other contributing factors, such as drug and alcohol use or smoking.

However, two ongoing randomized controlled trials, one in South America and one in the United States, may give more specific information.

"In these studies, pregnant women are randomized into two groups—one group has their periodontal disease treated during pregnancy and one group has it treated after pregnancy," Dr. Dasanayake said.

He added that several studies, including one of his own, have failed to find any association between oral bacteria and pregnancy outcome.

His study was performed in Sri Lanka with women who did not use tobacco, alcohol, or drugs because of cultural taboos and very low socioeconomic status. No association was seen in this group of women. ■

ENABLEX® (darifenacin)

Extended-release tablets

Rx only

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

INDICATIONS AND USAGE

ENABLEX® (darifenacin) extended-release tablets are indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency.

CONTRAINDICATIONS

ENABLEX® (darifenacin) extended-release tablets are contraindicated in patients with urinary retention, gastric retention or uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions. ENABLEX is also contraindicated in patients with known hypersensitivity to the drug or its ingredients.

PRECAUTIONS

General

Risk of Urinary Retention

ENABLEX® (darifenacin) extended-release tablets should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention.

Decreased Gastrointestinal Motility

ENABLEX should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention. ENABLEX, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as severe constipation, ulcerative colitis, and myasthenia gravis.

Controlled Narrow-Angle Glaucoma

ENABLEX should be used with caution in patients being treated for narrow-angle glaucoma and only where the potential benefits outweigh the risks.

Patients with Hepatic Impairment

There are no dosing adjustments for patients with mild hepatic impairment. The daily dose of ENABLEX should not exceed 7.5 mg for patients with moderate hepatic impairment. ENABLEX has not been studied in patients with severe hepatic impairment and therefore is not recommended for use in this patient population (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations and DOSAGE AND ADMINISTRATION in the full prescribing information).

Information for Patients

Patients should be informed that anticholinergic agents, such as ENABLEX, may produce clinically significant adverse effects related to anticholinergic pharmacological activity including constipation, urinary retention and blurred vision. Heat prostration (due to decreased sweating) can occur when anticholinergics such as ENABLEX are used in a hot environment. Because anticholinergics, such as ENABLEX, may produce dizziness or blurred vision, patients should be advised to exercise caution in decisions to engage in potentially dangerous activities until the drug's effects have been determined. Patients should read the patient information leaflet before starting therapy with ENABLEX.

ENABLEX extended-release tablets should be taken once daily with liquid. They may be taken with or without food, and should be swallowed whole and not chewed, divided or crushed.

Drug Interactions

The daily dose of ENABLEX should not exceed 7.5 mg when coadministered with potent CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir, neflavinir, clarithromycin and nefazodone) (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION in the full prescribing information).

Caution should be taken when ENABLEX is used concomitantly with medications that are predominantly metabolized by CYP2D6 and which have a narrow therapeutic window, such as flecainide, thioridazine and tricyclic antidepressants (see CLINICAL PHARMACOLOGY in the full prescribing information).

The concomitant use of ENABLEX with other anticholinergic agents may increase the frequency and/or severity of dry mouth, constipation, blurred vision and other anticholinergic pharmacological effects. Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to effects on gastrointestinal motility.

Drug Laboratory Test Interactions

Interactions between darifenacin and laboratory tests have not been studied.

Carcinogenesis/Mutagenesis/Impairment of Fertility

Carcinogenicity studies with darifenacin were conducted in mice and rats. No evidence of drug-related carcinogenicity was revealed in a 24-month study in mice at dietary doses up to 100 mg/kg/day or approximately 32 times the estimated human-free AUC_{0-24h} reached with 15 mg, the maximum recommended human dose (AUC at MRHD) and in a 24-month study in rats at doses up to 15 mg/kg/day or up to approximately 12 times the AUC at MRHD in female rats and approximately eight times the AUC at MRHD in male rats.

Darifenacin was not mutagenic in the bacterial mutation assays (Ames test) and the Chinese hamster ovary assay, and not clastogenic in the human lymphocyte assay, and the *in vivo* mouse bone marrow cytogenetics assay.

There was no evidence for effects on fertility in male or female rats treated at oral doses up to 50 mg/kg/day. Exposures in this study correspond to approximately 78 times the AUC at MRHD.

Pregnancy Category C

Darifenacin was not teratogenic in rats and rabbits at doses up to 50 and 30 mg/kg/day, respectively. At the dose of 50 mg/kg in rats, there was a delay in the ossification of the sacral and caudal vertebrae which was not observed at 10 mg/kg (approximately 13 times the AUC of free plasma concentration at MRHD). Exposure in this study at 50 mg/kg corresponds to approximately 59 times the AUC of free plasma concentration at MRHD. Dystocia was observed in dams at 10 mg/kg/day (17 times the AUC of free plasma concentration at MRHD). Slight developmental delays were observed in pups at this dose. At 3 mg/kg/day (five times the AUC of free plasma concentration at MRHD) there were no effects on dams or pups. At the dose of 30 mg/kg in rabbits, darifenacin was shown to increase post-implantation loss but not at 10 mg/kg (nine times the AUC of free plasma concentration at MRHD). Exposure to unbound drug at 30 mg/kg in this study corresponds to approximately 28 times the AUC at MRHD. In rabbits, dilated ureter and/or kidney pelvis was observed in offspring at 30 mg/kg/day and one case was observed at 10 mg/kg/day along with urinary bladder dilation consistent with pharmacological action of darifenacin. No effect was observed at 3 mg/kg/day (2.8 times the AUC of free plasma concentration at MRHD). There are no studies of darifenacin in pregnant women. Because animal reproduction studies are not always predictive of human response, ENABLEX should be used during pregnancy only if the benefit to the mother outweighs the potential risk to the fetus.

Nursing Mothers

Darifenacin is excreted into the milk of rats. It is not known whether darifenacin is excreted into human milk and therefore caution should be exercised before ENABLEX is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of ENABLEX in pediatric patients have not been established.

Geriatric Use

In the Phase III fixed-dose, placebo-controlled, clinical studies, 30% of patients treated with ENABLEX were over 65 years of age. No overall differences in safety or efficacy were observed between these patients (n=207) and younger patients <65 years (n=464). No dose adjustment is recommended for elderly patients (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations and CLINICAL STUDIES in the full prescribing information).

References: 1. Chapple CR, Yamashita T, Chess-Williams R. Muscarinic receptor subtypes and management of the overactive bladder. *Urology*. 2002;60(suppl 5A):82-89. 2. Federal Interagency Forum on Aging-Related Statistics. Older Americans 2000; key indicators of well-being, August 2000. Available at: <http://www.agingstats.gov/chartbook2000/healthstatus.html#indicator%2014>. Accessed November 4, 2004. 3. Feinberg M. The problems of anticholinergic adverse effects in older patients. *Drugs Aging*. 1993;3:335-348.

ADVERSE REACTIONS

During the clinical development of ENABLEX® (darifenacin) extended-release tablets, a total of 7,363 patients and volunteers were treated with doses of darifenacin from 3.75 mg to 75 mg once daily.

The safety of ENABLEX was evaluated in Phase II and III controlled clinical trials in a total of 8,830 patients, 6,001 of whom were treated with ENABLEX. Of this total, 1,069 patients participated in three, 12-week, Phase III, fixed-dose efficacy and safety studies. Of this total, 337 and 334 patients received ENABLEX 7.5 mg daily and 15 mg daily, respectively. In all long-term trials combined, 1,216 and 672 patients received treatment with ENABLEX for at least 24 and 52 weeks, respectively.

In all placebo-controlled trials combined, the incidence of serious adverse events for 7.5 mg, 15 mg and placebo was similar.

In all fixed-dose Phase III studies combined, 3.3% of patients treated with ENABLEX discontinued due to all adverse events versus 2.6% in placebo. Dry mouth leading to study discontinuation occurred in 0%, 0.9%, and 0% of patients treated with ENABLEX 7.5 mg daily, ENABLEX 15 mg daily and placebo, respectively. Constipation leading to study discontinuation occurred in 0.6%, 1.2%, and 0.3% of patients treated with ENABLEX 7.5 mg daily, ENABLEX 15 mg daily and placebo, respectively.

Table 4 lists the adverse events reported (regardless of causality) in 2% or more of patients treated with 7.5-mg or 15-mg ENABLEX extended-release tablets and greater than placebo in the three, fixed-dose, placebo-controlled Phase III studies (Studies 1, 2 and 3). Adverse events were reported by 54% and 66% of patients receiving 7.5 mg and 15 mg once-daily ENABLEX extended-release tablets, respectively, and by 49% of patients receiving placebo. In these studies, the most frequently reported adverse events were dry mouth and constipation. The majority of adverse events in ENABLEX-treated subjects were mild or moderate in severity and most occurred during the first two weeks of treatment.

Table 4
Incidence of Adverse Events* Reported in 2.0% of Patients Treated with ENABLEX® Extended-Release Tablets and More Frequent with ENABLEX® than with Placebo in Three, Fixed-Dose, Placebo-Controlled, Phase III Studies (Studies 1, 2, and 3)

Body System	Adverse Event	Percentage of Subjects with Adverse Event (%)		
		ENABLEX® 7.5 mg N = 337	ENABLEX® 15 mg N = 334	Placebo N = 388
Digestive	Dry Mouth	20.2	35.3	8.2
	Constipation	14.8	21.3	6.2
	Dyspepsia	2.7	8.4	2.6
	Abdominal Pain	2.4	3.9	0.5
	Nausea	2.7	1.5	1.5
Urogenital	Urinary Tract Infection	2.1	0.9	1.8
	Urinary Tract Infection	4.7	4.5	2.6
Nervous	Dizziness	0.9	2.1	1.3
	Asthma	1.5	2.7	1.3
Body as a Whole	Dry Eyes	1.5	2.1	0.5

*Regardless of causality

Other adverse events reported, regardless of causality, by ≥1% of ENABLEX patients in either the 7.5 mg or 15 mg once-daily darifenacin-dose groups in these fixed-dose, placebo-controlled Phase III studies include: abnormal vision, accidental injury, back pain, dry skin, flu syndrome, pain, hypertension, vomiting, peripheral edema, weight gain, arthralgia, bronchitis, pharyngitis, rhinitis, sinusitis, rash, pruritus, urinary tract disorder and vaginitis.

Study 4 was a 12-week, placebo-controlled, dose-titration regimen study in which ENABLEX was administered in accordance with dosing recommendations (see DOSAGE AND ADMINISTRATION in the full prescribing information). All patients initially received placebo or ENABLEX 7.5 mg daily, and after two weeks, patients and physicians were allowed to adjust upward to ENABLEX 15 mg if needed. In this study, the most commonly reported adverse events were also constipation and dry mouth. The incidence of discontinuation due to all adverse events was 3.1% and 6.7% for placebo and for ENABLEX, respectively. Table 5 lists the adverse events (regardless of causality) reported in >3% of patients treated with ENABLEX extended-release tablets and greater than placebo.

Table 5
Number (%) of Adverse Events* Reported in >3% of Patients Treated with ENABLEX® Extended-Release Tablets, and More Frequent with ENABLEX® than Placebo, in the Placebo-Controlled, Dose-Titration, Phase III Study (Study 4)

Adverse Event	ENABLEX® 7.5 mg/15 mg N = 268	Placebo N = 127
Constipation	56 (20.9%)	10 (7.9%)
Dry Mouth	50 (18.7%)	11 (8.7%)
Headache	18 (6.7%)	7 (5.5%)
Dyspepsia	12 (4.5%)	2 (1.6%)
Nausea	11 (4.1%)	2 (1.6%)
Urinary Tract Infection	10 (3.7%)	4 (3.1%)
Accidental Injury	8 (3.0%)	3 (2.4%)
Flu Syndrome	8 (3.0%)	3 (2.4%)

*Regardless of causality

Acute urinary retention (AUR) requiring treatment was reported in a total of 16 patients in the ENABLEX Phase I-III clinical trials. Of these 16 cases, seven were reported as serious adverse events, including one patient with detrusor hyperreflexia secondary to a stroke, one patient with benign prostatic hypertrophy (BPH), one patient with irritable bowel syndrome (IBS) and four OAB patients taking darifenacin 30 mg daily. Of the remaining nine cases, none were reported as serious adverse events. Three occurred in OAB patients taking the recommended doses, and two of these required bladder catheterization for 1-2 days.

Constipation was reported as a serious adverse event in six patients in the ENABLEX Phase I-III clinical trials, including one patient with benign prostatic hypertrophy (BPH), one OAB patient taking darifenacin 30 mg daily, and only one OAB patient taking the recommended doses. The latter patient was hospitalized for investigation with colonoscopy after reporting nine months of chronic constipation that was reported as being moderate in severity.

Storage

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

DECEMBER 2004 Printed in U.S.A.

Manufactured by:
Pfizer Inc.
Brooklyn, New York 11206

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936
©Novartis

T2004-49
5000213
5000214
5000215



Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

©2005 Novartis

3/05

C-ENA-1012