

Gestational Hypertension Risk Up With SDB

BY SUSAN LONDON

SEATTLE — Sleep-disordered breathing is an independent risk factor for gestational hypertension, and it also may confer an elevated risk of adverse fetal outcomes, according to Louise M. O'Brien, Ph.D., of the Sleep Disorders Center at the University of Michigan, Ann Arbor.

SDB, often diagnosed clinically as habitual snoring, is common in women of

childbearing age, with a reported prevalence of 5%-10%. Dr. O'Brien said at the annual meeting of the Associated Professional Sleep Societies. "This is probably the tip of the iceberg, because [many] women actually go undiagnosed."

The anatomic and physiological changes of pregnancy make pregnant women uniquely vulnerable to SDB, she noted. Indeed, studies show that the prevalence of habitual snoring rises with preg-

nancy, and ranges from 10% to nearly 40% of women during the third trimester. Data from a large ongoing study at the University of Michigan show that habitual snoring is markedly more common in unselected women during the third trimester of pregnancy than in nonpregnant women (35% vs. 7%). "What was particularly interesting is that this wasn't driven by women who were snoring before they got pregnant; in fact, the majority started ha-

bitually snoring only after they reached the second trimester," she said. This finding suggests that one-time screening shortly after conception will miss a lot of women.

Obesity appears to further elevate the risk. Compared with their normal-weight peers, obese women are more likely to have SDB in early pregnancy and to experience a worsening as pregnancy progresses (Chest 2001;120:1448-54). In addition, weight gain during pregnancy that exceeds the amount recommended by the Institute of Medicine independently predicts SDB (odds ratio, 1.9), based on the results of a study in 2009.

When it comes to maternal outcomes, evidence has linked SDB to both gestational hypertension and pre-eclampsia, according to Dr. O'Brien. Women who habitually snore during pregnancy are twice as likely to have gestational hypertension as their nonsnoring counterparts (Chest 2000;117:137-41). In addition, the upper airway has been found to be narrowed in pregnant women and even more so among pre-eclamptic pregnant women compared with their nonpregnant peers (Am. J. Respir. Crit. Care Med. 2003; 167:137-40).

Obesity complicates this picture because it also increases the risk of hypertension, she observed. But even after obesity is taken into account, habitual snoring remains an independent predictor of gestational hypertension (OR, 2.0), the 2009 study found. Moreover, there is an interaction whereby women who habitually snore and are obese have a particularly elevated risk (OR, 4.1).

On a brighter note, treatment of maternal SDB with continuous positive airway pressure (CPAP) may improve outcomes, Dr. O'Brien observed. For example, pregnant hypertensive women who snore and are at high risk of preeclampsia have a drop in blood pressure and maintain or reduce their dose of antihypertensive medication if they are treated with CPAP; in contrast, their blood pressure rises further and their dose of medication triples if they receive only usual care (Sleep Med. 2007;9:15-21). CPAP also appears to help restore the reduced fetal movements seen in women with preeclampsia (Sleep Med Clin. 2008;3:81-95).

Taken together, the evidence suggests that awareness of SDB during pregnancy is important, Dr. O'Brien stressed, yet obstetricians are generally unaware that their patients have habitual snoring or even apnea. "One, the women don't realize it's important to tell their physicians about it," she said. "And two, the obstetricians don't realize its important to ask about it."

Some surrogate measures of SDB may help obstetricians assess SDB-associated risk in their pregnant patients. For example, women are more likely to have gestational hypertension if they have a Mallampati grade of III or IV, indicating a crowded airway (OR, 1.9), or a neck circumference of 40 cm or greater (OR, 2.5), a 2008 study found. Dr. O'Brien reported that she had no conflicts of interest. ■



BRIEF SUMMARY

Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

GELNIQUE is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

GELNIQUE is for topical application only and should not be ingested.

CONTRAINDICATIONS

The use of GELNIQUE is contraindicated in the following conditions:

- Urinary retention
- Gastric retention
- Uncontrolled narrow-angle glaucoma
- Known hypersensitivity to GELNIQUE, including skin hypersensitivity

PRECAUTIONS

Urinary Retention

Administer GELNIQUE with caution in patients with clinically significant bladder outflow obstruction because of the risk of urinary retention.

Patients with Gastrointestinal Disorders

Administer GELNIQUE with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention.

GELNIQUE, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis or intestinal atony. GELNIQUE should be used with caution in patients who have gastroesophageal reflux and/or who are concurrently taking drugs (such as bisphosphonates) that can cause or exacerbate esophagitis.

Skin Hypersensitivity

In a controlled clinical trial of skin sensitization, 1 of 200 patients (0.5%) demonstrated skin hypersensitivity to GELNIQUE. Patients who develop skin hypersensitivity to GELNIQUE should discontinue drug treatment.

Skin Transference

Transfer of oxybutynin to another person can occur when vigorous skin-to-skin contact is made with the application site. To minimize the potential transfer of oxybutynin from GELNIQUE-treated skin to another person, patients should cover the application site with clothing after the gel has dried if direct skin-to-skin contact at the application site is anticipated. Patients should wash their hands immediately after application of GELNIQUE.

Flammable Gel

GELNIQUE is an alcohol-based gel and is therefore flammable. Avoid open fire or smoking until gel has dried.

Myasthenia Gravis

Administer GELNIQUE with caution in patients with myasthenia gravis, a disease characterized by decreased cholinergic activity at the neuromuscular junction.

ADVERSE REACTIONS

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 trial of another drug and may not reflect the rates observed in practice.

The safety of GELNIQUE was evaluated in 789 patients (389 randomized to GELNIQUE 1 g and 400 randomized to placebo) during a randomized, placebo-controlled, double-blind, 12-week clinical efficacy and safety study. A subset of these 789 patients (N=216) participated in the 14-week open-label safety extension that followed the placebo-controlled study. Of 216 patients in the safety extension, 107 were randomized to placebo gel during the double-blind, placebo-controlled 12-week study. In the combined double-blind, placebo-controlled study and the open-label safety extension, a total of 496 patients were exposed to at least one dose of GELNIQUE. Four hundred thirty-one (431) patients received

at least 12 weeks of GELNIQUE treatment and 85 patients received 26 weeks of GELNIQUE treatment. The study population primarily consisted of Caucasian women (approximately 90%) with an average age of 59 years who had overactive bladder with urge urinary incontinence.

Table 1 lists adverse events, regardless of causality, that were reported in the randomized, double-blind, placebo-controlled 12-week study at an incidence greater than placebo and in greater than 2% of patients treated with GELNIQUE.

Table 1: Common Adverse Events in the Randomized, Double-blind, Placebo-controlled 12-Week Study (>2% and > placebo)

Adverse Event	GELNIQUE 1 gram N=389 n (%)	Placebo N=400 n (%)
Dry mouth	29 (7.5)	11 (2.8)
Urinary tract infection	27 (6.9)	17 (4.3)
Application site reactions*	21 (5.4)	4 (1.0)
Upper respiratory tract infection	21 (5.4)	20 (5.0)
Dizziness	11 (2.8)	4 (1.0)
Nasopharyngitis	11 (2.8)	9 (2.3)
Fatigue	8 (2.1)	4 (1.0)
Gastroenteritis viral	8 (2.1)	7 (1.8)

*Includes application site pruritus, dermatitis, papules, anesthesia, erythema, irritation, pain and papules

The most common adverse reactions, defined as adverse events judged by the investigator to be reasonably associated with the use of study drug, that were reported in ≥ 1% of GELNIQUE-treated patients were dry mouth (6.9%), application site reactions (5.4%), dizziness (1.5%), headache (1.5%), constipation (1.3%), and pruritus (1.3%). Application site pruritus (2.1%) and application site dermatitis (1.8%) were the most commonly reported application site reactions. A majority of treatment-related adverse events were described as mild or moderate in intensity, except for two patients reporting severe headache. No serious adverse events were judged by the investigator to be treatment-related during the randomized, double-blind, placebo-controlled 12-week study. The most common adverse reaction leading to drug discontinuation was application site reaction (0.8% with GELNIQUE versus 0.3% with placebo).

The most common adverse reactions reported during the 14-week open-label extension study were application site reactions (6.0%) and dry mouth (1.9%). The most common reason for premature discontinuation was application site reactions (9 patients or 4.2%). Two of these 9 patients experienced application site reactions of severe intensity (dermatitis, urticaria, and erythema).

DRUG INTERACTIONS

No specific drug-drug interaction studies have been performed with GELNIQUE.

Use With Other Anticholinergics

The concomitant use of GELNIQUE with other anticholinergic (antimuscarinic) agents may increase the frequency and/or severity of dry mouth, constipation, blurred vision, somnolence and other anticholinergic pharmacological effects.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies of topical or oral oxybutynin use in pregnant women. Subcutaneous administration to rats at doses up to 25 mg/kg (approximately 50 times the human exposure based on surface area) and to rabbits at doses up to 0.4 mg/kg (approximately 1 times the human exposure) revealed no evidence of harm to the fetus due to oxybutynin chloride. The safety of GELNIQUE administration to women who are or who may become pregnant has not been established. Therefore, GELNIQUE should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

Nursing Mothers

It is not known whether oxybutynin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when GELNIQUE is administered to a nursing woman.

Geriatric Use

Of the 496 patients exposed to GELNIQUE in the randomized, double-blind, placebo-controlled 12-week study and the 14-week safety extension study, 188 patients (38%) were 65 years of age and older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Pediatric Patients

The pharmacokinetics of oxybutynin and N-desethyloxybutynin have not been evaluated in individuals younger than 18 years of age.

Renal Impairment

There is no experience with the use of GELNIQUE in patients with renal impairment.

Hepatic Impairment

There is no experience with the use of GELNIQUE in patients with hepatic impairment.

Race

The effect of race on the pharmacokinetics of GELNIQUE has not been studied.

Gender

Available data suggest that there are no significant differences in the pharmacokinetics of oxybutynin based on gender in healthy volunteers following administration of GELNIQUE.

Use of Sunscreen

The effect of sunscreen on the absorption of oxybutynin when applied 30 minutes before or 30 minutes after GELNIQUE application was evaluated in a single-dose randomized crossover study (N=16). Concomitant application of sunscreen, either before or after GELNIQUE application, had no effect on the systemic exposure of oxybutynin.

Showering

The effect of showering on the absorption of oxybutynin was evaluated in a randomized, steady-state crossover study under conditions of no shower, or showering 1, 2 or 6 hours after GELNIQUE application (N=20). The results of the study indicate that showering after one hour does not affect the overall systemic exposure to oxybutynin.

OVERDOSAGE

Overdosage with oxybutynin has been associated with anticholinergic effects including central nervous system excitation, flushing, fever, dehydration, cardiac arrhythmia, vomiting, and urinary retention. Oral ingestion of 100 mg oxybutynin chloride in association with alcohol has been reported in a 13-year-old boy who experienced memory loss, and in a 34-year-old woman who developed stupor, followed by disorientation and agitation on awakening, dilated pupils, dry skin, cardiac arrhythmia, and retention of urine. Both patients recovered fully with symptomatic treatment.

Plasma concentrations of oxybutynin begin to decline 24 hours after GELNIQUE application. If overexposure occurs, monitor patients until symptoms resolve.

Keep out of reach of children.

Storage

Store at room temperature, 25°C (77°F). Temporary storage between 15 - 30°C (59 - 86°F) is also permitted. Keep GELNIQUE and all medications in a safe, secure place and out of the reach of children.

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