

**Second branchial fistulas present as a tiny hole in the neck and can extend up to the tonsillar fossae.**



COURTESY DR. SETH M. PRANSKY

# History Key to Diagnosis Of Pediatric Neck Masses

BY DOUG BRUNK

SAN DIEGO — Be thorough in your history taking when infants or children present with a neck mass, Dr. Seth M. Pransky advised.

“We want to know how long it’s been there and what the associated symptoms are,” he said at a meeting sponsored by

Rady Children’s Hospital and the American Academy of Pediatrics. “Was there an antecedent respiratory infection or antecedent trauma? Has it become bigger or smaller, or has it remained the same size? What have the child’s exposures been in terms of ill contacts, animals, and food?”

Such questions can guide you in determining what the correct diagnosis might be, said Dr. Pransky, director of pediatric otolaryngology at Children’s Specialists Medical Group, San Diego.

An estimated 55% of pediatric neck masses are congenital, followed by acquired forms that include infectious, neoplastic, and inflammatory processes.

Branchial cleft anomalies are some of the most common types of congenital neck masses. These typically present as sinus tracts or fistulas detected at birth, with an opening in the skin with subsequent discharge that can be mucoid or mucopurulent. They may also present as cysts that enlarge gradually and present in the second or third decade of life.

A common type of branchial cleft anomaly is a preauricular anomaly that “begins as a pit in the preauricular region and often extends via a sinus tract down to a cystic dilatation almost always at the root of the helix,” Dr. Pransky said. Surgical excision is advised if there is a discharge. “If there’s no discharge we’ll leave it alone.”

First branchial arch anomalies can extend deeply into the neck. They present either as parallel to the external auditory canal or in the upper neck, below the angle of the mandible. “These are a lot more challenging to manage surgically,” he said. “Fortunately they are rare.”

Second branchial anomalies occur in the mid to lower portion of the neck along the anterior sternocleidomastoid muscle. Fistulas present as a tiny hole in the neck and can extend up to the tonsillar fossae. “If you milk it you’ll see strandy secretions, which are probably mucus,” he said. “I’m not comfortable with just taking out the neck portion of these lesions. I also take out the tonsil in conjunction with the entire fistulous tract.”

Second branchial cysts “frequently present as a soft swelling, not as an infectious problem,” he said. Third/fourth branchial cleft anomalies are rare and may present as an infectious swelling low in the floor of the neck laterally or in the anterior neck adjacent to the thyroid gland. “When you aspirate the lesion, you’re going to get a mixed polymicrobial infection,” Dr. Pransky said. “That’s because you’re getting organisms from the hypopharynx.”

These anomalies may also present as acute thyroiditis. “That tract goes from the pyriform fossa in the hypopharynx through the thyroid gland into the neck,” he said. “When a 5- or 6-year-old presents with a thyroiditis, my first thought is that they have a branchial or branchial four anomaly.”

Dr. Pransky disclosed no conflicts of interest.

## TOVIAZ™ (fesoterodine fumarate) extended release tablets

R<sub>x</sub> only

### BRIEF SUMMARY OF PRESCRIBING INFORMATION.

The following is a brief summary only; see full Prescribing Information for complete product information.

### INDICATIONS AND USAGE

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

### CONTRAINDICATIONS

Toviaz is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma. Toviaz is also contraindicated in patients with known hypersensitivity to the drug or its ingredients.

### PRECAUTIONS

#### General

**Bladder Outlet Obstruction:** Toviaz should be administered with caution to patients with clinically significant bladder outlet obstruction because of the risk of urinary retention (see **CONTRAINDICATIONS**).

**Decreased Gastrointestinal Motility:** Toviaz, like other antimuscarinic drugs, should be used with caution in patients with decreased gastrointestinal motility, such as those with severe constipation.

**Controlled Narrow-Angle Glaucoma:** Toviaz should be used with caution in patients being treated for narrow-angle glaucoma, and only where the potential benefits outweigh the risks (see **CONTRAINDICATIONS**).

**Reduced Hepatic Function:** There are no dosing adjustments for patients with mild or moderate hepatic impairment. Toviaz 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** in full prescribing information and **DOSAGE AND ADMINISTRATION**).

**Myasthenia Gravis:** Toviaz should be used with caution in patients with myasthenia gravis, a disease characterized by decreased cholinergic activity at the neuromuscular junction.

**Reduced Renal Function:** There are no dosing adjustments for patients with mild or moderate renal insufficiency. Doses of Toviaz greater than 4 mg are not recommended in patients with severe renal insufficiency (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations** in full prescribing information and **DOSAGE AND ADMINISTRATION**).

**Concomitant Administration with CYP3A4 Inhibitors:** Doses of Toviaz greater than 4 mg are not recommended in patients taking a potent CYP3A4 inhibitor (e.g. ketoconazole, itraconazole, clarithromycin).

In patients taking weak or moderate CYP3A4 inhibitors (e.g. erythromycin), careful assessment of tolerability at the 4 mg daily dose is advised prior to increasing the daily dose to 8 mg. While this specific interaction potential was not examined by clinical study, some pharmacokinetic interaction is expected, albeit less than that observed with potent CYP3A4 inhibitors (see **CLINICAL PHARMACOLOGY, Drug-Drug Interactions** in full prescribing information and **DOSAGE AND ADMINISTRATION**).

### Information for Patients

Patients should be informed that Toviaz, like other antimuscarinic agents, may produce clinically significant adverse effects related to antimuscarinic pharmacological activity including constipation and urinary retention. Toviaz, like other antimuscarinics, may be associated with blurred vision, therefore, patients should be advised to exercise caution until the drug’s effects on the patient have been determined. Heat prostration (due to decreased sweating) can occur when Toviaz, like other antimuscarinic drugs, is used in a hot environment. Patients should also be informed that alcohol may enhance the drowsiness caused by Toviaz, like other anticholinergic agents. Patients should read the patient leaflet entitled “Patient Information TOVIAZ” before starting therapy with Toviaz.

### Drug Interactions

Coadministration of Toviaz with other antimuscarinic agents that produce dry mouth, constipation, urinary retention, and other anticholinergic pharmacological effects may increase the frequency and/or severity of such effects. Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. Also see **PRECAUTIONS, Concomitant Administration with CYP3A4 Inhibitors**.

### Drug-Laboratory Test Interactions

Interactions between Toviaz and laboratory tests have not been studied.

### Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of drug-related carcinogenicity was found in 24-month studies with oral administration to mice and rats. The highest tolerated doses in mice (females 45 to 60 mg/kg/day, males 30 to 45 mg/kg/day) correspond to 11- to 19-fold (females) and 4- to 9-fold (males) the estimated human AUC values reached with fesoterodine 8 mg, which is the Maximum Recommended Human Dose (MRHD). In rats, the highest tolerated dose (45 to 60 mg/kg/day) corresponds to 3- to 8-fold (females) and 3- to 14-fold (males), the estimated human AUC at the MRHD.

Fesoterodine was not mutagenic or genotoxic in vitro (Ames tests, chromosome aberration tests) or in vivo (mouse micronucleus test).

Fesoterodine had no effect on reproductive function, fertility, or early embryonic development of the fetus at non-maternally toxic doses in mice. The maternal No-Observed-Effect Level (NOEL) and the NOEL for effects on reproduction and early embryonic development were both 15 mg/kg/day. Based on AUC, the systemic exposure was 0.6- to 1.5-fold higher in mice than in humans at the MRHD, whereas based on peak plasma concentrations, the exposure in mice was 5- to 9-fold higher. The Lowest-Observed-Effect Level (LOEL) for maternal toxicity was 45 mg/kg/day.

### Pregnancy

#### Pregnancy Category C

Reproduction studies have been performed in mice and rabbits. No dose-related teratogenicity was observed at oral doses up to 75 mg/kg/day in mice (6 to 27 times the expected exposure at the MRHD based on AUC and greater than 77 times the expected  $C_{max}$ ) and up to 27 mg/kg/day in rabbits (3- to 11-fold by AUC and 19- to 62-fold by  $C_{max}$ ) or at subcutaneous doses up to 4.5 mg/kg/day in rabbits (9- to 11-fold by AUC and 43- to 56-fold by  $C_{max}$ ). In mice treated orally with 75 mg/kg/day (6- to 27-times the expected exposure at the MRHD based on AUC and greater than 77-times the expected  $C_{max}$ ), increased resorptions and decreased live fetuses were observed. One fetus with cleft palate was observed at each dose (15, 45 and 75 mg/kg/day), at an incidence within the background historical range. In rabbits treated orally with 27 mg/kg/day (3- to 11-fold by AUC and 19- to 62-fold by  $C_{max}$ ), incompletely ossified sternebrae (retardation of bone development) were observed in fetuses. In rabbits treated by subcutaneous (sc) administration with 4.5 mg/kg/day (9- to 11-fold by AUC and 43- to 53-fold by  $C_{max}$ ), maternal toxicity and incompletely ossified sternebrae were observed in fetuses (at an incidence within the background historical range). At 1.5 mg/kg/day s.c., (3-fold by AUC and 11- to 13-fold by  $C_{max}$ ), decreased maternal food consumption in the absence of any fetal effects was observed. Oral administration of 30 mg/kg/day fesoterodine to mice in a pre- and post-natal development study resulted in decreased body weight of the dams and delayed ear opening of the pups. No effects were noted on mating and reproduction of the F<sub>1</sub> dams or on the F<sub>2</sub> offspring.

There are no adequate and well-controlled studies using Toviaz in pregnant women. Therefore, Toviaz should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

### Nursing Mothers

It is not known whether fesoterodine is excreted in human milk. Toviaz should not be administered during nursing unless the potential benefit outweighs the potential risk to the neonate.

### Pediatric Use

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

### Geriatric Use

Of 1567 patients who received Toviaz 4 mg/day or 8 mg/day in the Phase 2 and 3, placebo-controlled, efficacy and safety studies, 515 (33%) were 65 years of age or older, and 140 (9%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between patients younger than 65 years of age and those 65 years of age or older in these studies; however, the incidence of antimuscarinic adverse events, including dry mouth, constipation, dyspepsia, increase in residual urine, dizziness (at 8 mg only) and urinary tract infection, was higher in patients 75 years of age and older as compared to younger patients (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations** and **CLINICAL STUDIES** in full prescribing information and **ADVERSE REACTIONS**).

### ADVERSE REACTIONS

The safety of Toviaz was evaluated in Phase 2 and 3 controlled trials in a total of 2859 patients with overactive bladder of which 2288 were treated with fesoterodine. Of this total, 782 received Toviaz 4 mg/day, and 785 received Toviaz 8 mg/day in Phase 2 or 3 studies with treatment periods of 8 or 12 weeks. Approximately 80% of these patients had >10 weeks exposure to Toviaz in these trials.

A total of 1964 patients participated in two 12-week, Phase 3 efficacy and safety studies and subsequent open-label extension studies. In these 2 studies combined, 554 patients received Toviaz 4 mg/day and 566 patients received Toviaz 8 mg/day.

In Phase 2 and 3 placebo-controlled trials combined, the incidences of serious adverse events in patients receiving placebo, Toviaz 4 mg, and Toviaz 8 mg were 1.9%, 3.5%, and 2.9%, respectively. All serious adverse events were judged to be not related or unlikely to be related to study medication by the investigator, except for four patients receiving Toviaz who reported one serious adverse event each: angina, chest pain, gastroenteritis, and QT prolongation on ECG.

The most commonly reported adverse event in patients treated with Toviaz was dry mouth. The incidence of dry mouth was higher in those taking 8 mg/day (35%) and in those taking 4 mg/day (19%), as compared to placebo (7%). Dry mouth led to discontinuation in 0.4%, 0.4%, and 0.8% of patients receiving placebo, Toviaz 4 mg, and Toviaz 8 mg, respectively. For those patients who reported dry mouth, most had their first occurrence of the event within the first month of treatment.

The second most commonly reported adverse event was constipation. The incidence of constipation was 2% in those taking placebo, 4% in those taking 4 mg/day, and 6% in those taking 8 mg.

Table 3 lists adverse events, regardless of causality, that were reported in the combined Phase 3, randomized, placebo-controlled trials at an incidence greater than placebo and in 1% or more of patients treated with Toviaz 4 mg or 8 mg once daily for up to 12 weeks.

**Table 3. Adverse events with an incidence exceeding the placebo rate and reported by ≥1% of patients from double-blind, placebo-controlled Phase 3 trials of 12 weeks’ treatment duration**

System organ class	Preferred term	Placebo N=554 %	Toviaz 4 mg/day N=554 %	Toviaz 8 mg/day N=566 %
Gastrointestinal disorders	Dry mouth	7.0	18.8	34.6
	Constipation	2.0	4.2	6.0
	Dyspepsia	0.5	1.6	2.3
	Nausea	1.3	0.7	1.9
Infections	Abdominal pain upper	0.5	1.1	0.5
	Urinary tract infection	3.1	3.2	4.2
Eye disorders	Upper respiratory tract infection	2.2	2.5	1.8
	Dry eyes	0	1.4	3.7
Renal and urinary disorders	Dysuria	0.7	1.3	1.6
	Urinary retention	0.2	1.1	1.4
Respiratory disorders	Cough	0.5	1.6	0.9
	Dry throat	0.4	0.9	2.3
General disorders	Edema peripheral	0.7	0.7	1.2
Musculoskeletal disorders	Back pain	0.4	2.0	0.9
Psychiatric disorders	Insomnia	0.5	1.3	0.4
Investigations	ALT increased	0.9	0.5	1.2
	GGT increased	0.4	0.4	1.2
Skin disorders	Rash	0.5	0.7	1.1

ALT=alanine aminotransferase, GGT=gamma glutamyltransferase

Patients also received Toviaz for up to three years in open-label extension phases of one Phase 2 and two Phase 3 controlled trials. In all open-label trials combined, 857, 701, 529, and 105 patients received Toviaz for at least 6 months, 1 year, 2 years, and 3 years respectively. The adverse events observed during long-term, open-label studies were similar to those observed in the 12-week, placebo-controlled studies, and included dry mouth, constipation, dry eyes, dyspepsia and abdominal pain. Similar to the controlled studies, most adverse events of dry mouth and constipation were mild to moderate in intensity. Serious adverse events, judged to be at least possibly related to study medication by the investigator, and reported more than once during the open-label treatment period of up to 3 years included urinary retention (3 cases), diverticulitis (3 cases), constipation (2 cases), irritable bowel syndrome (2 cases), and electrocardiogram QT corrected interval prolongation (2 cases).

### OVERDOSAGE

Overdosage with Toviaz can result in severe anticholinergic effects. Treatment should be symptomatic and supportive. In the event of overdosage, ECG monitoring is recommended.

### DOSAGE AND ADMINISTRATION

The recommended starting dose of Toviaz is 4 mg once daily. Based upon individual response and tolerability, the dose may be increased to 8 mg once daily.

The daily dose of Toviaz should not exceed 4 mg in the following populations:

- Patients with severe renal insufficiency ( $CL_{Cr} < 30$  mL/min).
- Patients taking potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, and clarithromycin.

Toviaz is not recommended for use in patients with severe hepatic impairment (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations** in full prescribing information and **PRECAUTIONS**).

Toviaz should be taken with liquid and swallowed whole. Toviaz can be administered with or without food, and should not be chewed, divided, or crushed.

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