



CPA meningioma with internal auditory canal extension seen on axial MRI.



Complete resection of the meningioma is evident on postoperative CT scan.

PHOTOS COURTESY DR. JOHN P. LEONETTI

# Meningiomas Require a Wider Surgical Approach

BY PATRICE WENDLING  
Chicago Bureau

LOS ANGELES — Large meningiomas can be resected with good long-term outcomes and without damage to the facial nerve using a combined retrosigmoid-transpetrosal-transchochlear approach, Rita M. Schuman, M.D., reported.

Large meningiomas located in the space between the cerebellum and the pons can originate from any area of the dura on the posterior surface of the petrous bone. Tumor removal is surgically challenging due to tumor vascularity, neural attachment, and brainstem compression.

Surgeons at the Loyola Center for Cranial Base Surgery in Maywood, Ill., combined several traditional approaches in a single-stage procedure, employing both retrosigmoid and presigmoid dural openings in 29 patients with large meningiomas of the cerebellopontine angle. The combined approach allows for wider access.

The approach was selected because of the combination of poor hearing and large tumor size among the patients, Dr. Schuman, a resident, said at the annual meeting of the American Academy of Otolaryngology-Head and Neck Surgery Foundation.

Tumors ranged in size from 3 cm to 4 cm (8 cases), 4.1 cm to 5 cm (14), 5.1 cm to 6 cm (4), and 6 cm or larger (3), according to a chart review from July 1995 to July 2004.

The most common presenting symptoms were hearing loss (25 patients) and unilateral tinnitus (22 patients). Only six patients had no cranial nerve involvement upon presentation.

Complete tumor removal was achieved in 19 of 29 (66%) patients, near-total removal in 7 (24%), and subtotal removal in 3 (10%).

Postoperative sequelae included three cases of facial paralysis (10.3%), one case of cranial nerve grade 5 deficit (3.4%), two cranial nerve grade 6 deficits (6.9%), one case of vocal cord paralysis (3.4%), and one of cerebrospinal fluid fistula (3.4%).

The facial nerve was preserved despite the surgery in 26 of 29 patients. At the 2-year follow-up, 20 of the patients with an intact facial nerve had good function in that nerve, and 6 had adequate function.

With an average of 4.6 years follow-up, there was no residual tumor in 19 patients; the tumors were stable in another six patients, and there were signs of tumor regrowth in four (13.8%) patients.

"[The] three different approaches together [provide] the neurosurgeon with a wider lateral access to the tumor, and long-term follow-up shows the recurrence rate is low, and the total tumor removal rate is high," lead author John P. Leonetti, M.D., director of the Center and professor of otolaryngology at Loyola University, said in an interview.

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#### INDICATIONS AND USAGE

RAZADYNE<sup>ER</sup>/RAZADYNE<sup>TM</sup> (galantamine hydrobromide) is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

#### CONTRAINDICATIONS

RAZADYNE<sup>ER</sup>/RAZADYNE<sup>TM</sup> (galantamine hydrobromide) is contraindicated in patients with known hypersensitivity to galantamine hydrobromide or to any excipients used in the formulation.

#### WARNINGS

**Anesthesia:** Galantamine, as a cholinesterase inhibitor, is likely to exaggerate the neuromuscular blocking effects of succinylcholine-type and similar neuromuscular blocking agents during anesthesia. **Cardiovascular Conditions:** Because of their pharmacological action, cholinesterase inhibitors have vagotonic effects on the sinoatrial and atrioventricular nodes, leading to bradycardia and AV block. These actions may be particularly important to patients with supraventricular cardiac conduction disorders or to patients taking other drugs concomitantly that significantly slow heart rate. Postmarketing surveillance of marketed anticholinesterase inhibitors has shown, however, that bradycardia and all types of heart block have been reported in patients both with and without known underlying cardiac conduction abnormalities. Therefore all patients should be considered at risk for adverse effects on cardiac conduction. In randomized controlled trials, bradycardia was reported more frequently in galantamine-treated patients than in placebo-treated patients, but was rarely severe and rarely led to treatment discontinuation. The overall frequency of this event was 2-3% for galantamine doses up to 24 mg/day compared with <1% for placebo. No increased incidence of heart block was observed at the recommended doses. Patients treated with galantamine up to 24 mg/day using the recommended dosing schedule showed a dose-related increase in risk of syncope (placebo 0.7% [2/286]; 4 mg BID 0.4% [3/692]; 8 mg BID 1.3% [7/552]; 12 mg BID 2.2% [6/273]). **Gastrointestinal Conditions:** Through their primary action, cholinomimetics may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those with an increased risk for developing ulcers, e.g., those with a history of ulcer disease or patients using concurrent nonsteroidal anti-inflammatory drugs (NSAIDs). Clinical studies of RAZADYNE<sup>TM</sup> (galantamine hydrobromide) have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding. RAZADYNE<sup>TM</sup>, as a predictable consequence of its pharmacological properties, has been shown to produce nausea, vomiting, diarrhea, anorexia, and weight loss (see ADVERSE REACTIONS). **Genitourinary:** Although this was not observed in clinical trials with RAZADYNE<sup>TM</sup>, cholinomimetics may cause bladder outflow obstruction. **Neurological Conditions:** Seizures: Cholinesterase inhibitors are believed to have some potential to cause generalized convulsions. However, seizure activity may also be a manifestation of Alzheimer's disease. In clinical trials, there was no increase in the incidence of convulsions with RAZADYNE<sup>TM</sup>, compared to placebo. **Pulmonary Conditions:** Because of its cholinomimetic action, galantamine should be prescribed with care to patients with a history of severe asthma or obstructive pulmonary disease.

#### PRECAUTIONS

**Information for Patients and Caregivers:** Caregivers should be instructed about the recommended dosage and administration of RAZADYNE<sup>ER</sup>/RAZADYNE<sup>TM</sup> (galantamine hydrobromide), RAZADYNE<sup>ER</sup> Extended-Release Capsules should be administered once daily in the morning, preferably with food (although not required), RAZADYNE<sup>TM</sup> Tablets and Oral Solution should be administered twice per day, preferably with the morning and evening meals. Dose escalation (dose increases) should follow a minimum of four weeks at prior dose. Patients and caregivers should be advised that the most frequent adverse events associated with use of the drug can be minimized by following the recommended dosage and administration. Patients and caregivers should be advised to ensure adequate fluid intake during treatment. If therapy has been interrupted for several days or longer, the patient should be restarted at the lowest dose and the dose escalated to the current dose. Caregivers should be instructed in the correct procedure for administering RAZADYNE<sup>TM</sup> Oral Solution. In addition, they should be informed of the existence of an Instruction Sheet (included with the product) describing how the solution is to be administered. They should be urged to read this sheet prior to administering RAZADYNE<sup>TM</sup> Oral Solution. Caregivers should direct questions about the administration of the solution to either their physician or pharmacist.

**Deaths in Subjects with Mild Cognitive Impairment (MCI):** In two randomized placebo controlled trials of 2 years duration in subjects with mild cognitive impairment (MCI), a total of 13 subjects on RAZADYNE<sup>TM</sup> (n=1026) and 1 subject on placebo (n=1022) died. The deaths were due to various causes which could be expected in an elderly population; about half of the RAZADYNE<sup>TM</sup> deaths appeared to result from various vascular causes (myocardial infarction, stroke, and sudden death). Although the difference in mortality between RAZADYNE<sup>TM</sup> and placebo-treated groups in these two studies was significant, the results are highly discrepant with other studies of RAZADYNE<sup>TM</sup>. Specifically, in these two MCI studies, the mortality rate in the placebo-treated subjects was markedly lower than the rate in placebo-treated patients in trials of RAZADYNE<sup>TM</sup> in Alzheimer's disease or other dementias (0.7 per 1000 person years compared to 22-61 per 1000 person years, respectively). Although the mortality rate in the RAZADYNE<sup>TM</sup>-treated MCI subjects was also lower than that observed in RAZADYNE<sup>TM</sup>-treated patients in Alzheimer's disease and other dementia trials (10.2 per 1000 person years compared to 23-31 per 1000 person years, respectively), the relative difference was much less. When the Alzheimer's disease and other dementia studies were pooled (n=6000), the mortality rate in the placebo group numerically exceeded that in the RAZADYNE<sup>TM</sup> group. Furthermore, in the MCI studies, no subjects in the placebo group died after 6 months, a highly unexpected finding in this population. Individuals with mild cognitive impairment demonstrate isolated memory impairment greater than expected for their age and education, but do not meet current diagnostic criteria for Alzheimer's disease. **Special Populations** Hepatic Impairment: In patients with moderately impaired hepatic function, dose titration should proceed cautiously (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION in the full PI). The use of RAZADYNE<sup>TM</sup> in patients with severe hepatic impairment is not recommended. Renal Impairment: In patients with moderately impaired renal function, dose titration should proceed cautiously (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION in the full PI). In patients with severely impaired renal function (CL<sub>CR</sub> < 9 mL/min) the use of RAZADYNE<sup>TM</sup> is not recommended. **Drug-Drug Interactions (see also CLINICAL PHARMACOLOGY, Drug-Drug Interactions in the full PI)** Use With Anticholinergics: RAZADYNE<sup>TM</sup> has the potential to interfere with the activity of anticholinergic medications. Use With Cholinomimetics and Other Cholinesterase Inhibitors: A synergistic effect is expected when cholinesterase inhibitors are given concurrently with succinylcholine, other cholinesterase inhibitors, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

A) Effect of Other Drugs on Galantamine: *In vitro* – CYP3A4 and CYP2D6 are the major enzymes involved in the metabolism of galantamine. CYP3A4 mediates the formation of galantamine-N-oxide; CYP2D6 leads to the formation of O-desmethyl-galantamine. Because galantamine is also glucuronidated and excreted unchanged, no single pathway appears predominant. *In vivo* – Cimetidine and Ranitidine: Galantamine was administered as a single dose of 4 mg on day 2 of a 3-day treatment with either cimetidine (800 mg daily) or ranitidine (300 mg daily). Cimetidine increased the bioavailability of galantamine by approximately 16%. Ranitidine had no effect on the PK of galantamine. **Ketoconazole:** Ketoconazole, a strong inhibitor of CYP3A4 and an inhibitor of CYP2D6, at a dose of 200 mg BID for 4 days, increased the AUC of galantamine by 30%. **Erythromycin:** Erythromycin, a moderate inhibitor of CYP3A4 at a dose of 500 mg QID for 4 days, affected the AUC of galantamine minimally (10% increase). **Paroxetine:** Paroxetine, a strong inhibitor of CYP2D6, at 20 mg/day for 16 days, increased the oral bioavailability of galantamine by about 40%.

B) Effect of Galantamine on Other Drugs: *In vitro* – Galantamine did not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6 or CYP2E1. This indicates that the inhibitory potential of galantamine towards the major forms of cytochrome P450 is very low. *In vivo* – Warfarin: Galantamine at 24 mg/day had no effect on the pharmacokinetics of R- and S-warfarin (25 mg single dose) or on the prothrombin time. The protein binding of warfarin was unaffected by galantamine. **Digoxin:** Galantamine at 24 mg/day had no effect on the steady-state pharmacokinetics of digoxin (0.375 mg once daily) when they were coadministered. In this study, however, one healthy subject was hospitalized for 2<sup>nd</sup> and 3<sup>rd</sup> degree heart block and bradycardia. **Carcinogenesis, Mutagenesis and Impairment of Fertility:** In a 24-month oral carcinogenicity study in rats, a slight increase in endometrial adenocarcinomas was observed at 10 mg/kg/day (4 times the Maximum Recommended Human Dose [MRHD]) on a mg/m<sup>2</sup> basis or 6 times on an exposure [AUC] basis) and 30 mg/kg/day (12 times MRHD on a mg/m<sup>2</sup> basis or 19 times on an AUC basis). No increase in neoplastic changes was observed in females at 2.5 mg/kg/day (equivalent to the MRHD on a mg/m<sup>2</sup> basis or 2 times on an AUC basis) or in males up to the highest dose tested of 30 mg/kg/day (12 times the MRHD on a mg/m<sup>2</sup> and AUC basis). Galantamine was not carcinogenic in a 6-month oral carcinogenicity study in transgenic (P 53-deficient) mice up to 20 mg/kg/day, or in a 24-month oral carcinogenicity study in male and female mice up to 10 mg/kg/day (2 times the MRHD on a mg/m<sup>2</sup> basis and equivalent on an AUC basis). Galantamine produced no evidence of genotoxic potential when evaluated in the *in vitro* Ames S. typhimurium or E. coli reverse mutation assay, *in vitro* mouse

lymphoma assay, *in vivo* micronucleus test in mice, or *in vitro* chromosome aberration assay in Chinese hamster ovary cells. No impairment of fertility was seen in rats given up to 16 mg/kg/day (7 times the MRHD on a mg/m<sup>2</sup> basis) for 14 days prior to mating in females and for 60 days prior to mating in males. **Pregnancy:** Pregnancy Category B: In a study in which rats were dosed from day 14 (females) or day 60 (males) prior to mating through the period of organogenesis, a slightly increased incidence of skeletal variations was observed at doses of 8 mg/kg/day (3 times the Maximum Recommended Human Dose [MRHD] on a mg/m<sup>2</sup> basis) and 16 mg/kg/day. In a study in which pregnant rats were dosed from the beginning of organogenesis through day 21 post-partum, pup weights were decreased at 8 and 16 mg/kg/day, but no adverse effects on other postnatal developmental parameters were seen. The doses causing the above effects in rats produced slight maternal toxicity. No major malformations were caused in rats given up to 16 mg/kg/day. No drug related teratogenic effects were observed in rabbits given up to 40 mg/kg/day (32 times the MRHD on a mg/m<sup>2</sup> basis) during the period of organogenesis. There are no adequate and well-controlled studies of RAZADYNE<sup>TM</sup> in pregnant women. RAZADYNE<sup>TM</sup> should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** It is not known whether galantamine is excreted in human breast milk. RAZADYNE<sup>TM</sup> has no indication for use in nursing mothers. **Pediatric Use:** There are no adequate and well-controlled trials documenting the safety and efficacy of galantamine in any illness occurring in children. Therefore, use of RAZADYNE<sup>TM</sup> in children is not recommended.

#### ADVERSE REACTIONS

**Pre-Marketing Clinical Trial Experience:** The specific adverse event data described in this section are based on studies of the immediate-release tablet formulation. In clinical trials, once-daily treatment with RAZADYNE<sup>ER</sup> (galantamine hydrobromide) Extended-Release Capsules was well tolerated and adverse events were similar to those seen with RAZADYNE<sup>TM</sup> Tablets. Adverse Events Leading to Discontinuation: In two large scale, placebo-controlled trials of 6 months duration in which patients were titrated weekly from 8 to 16 to 24, and to 32 mg/day, the risk of discontinuation because of an adverse event in the galantamine group exceeded that in the placebo group by about threefold. In contrast, in a 5-month trial with escalation of the dose by 8 mg/day every 4 weeks, the overall risk of discontinuation because of an adverse event was 7%, 7%, and 10% for the placebo, galantamine 16 mg/day, and galantamine 24 mg/day groups, respectively, with gastrointestinal adverse effects the principle reason for discontinuing galantamine. Table 1 shows the most frequent adverse events leading to discontinuation in this study.

**Table 1: Most Frequent Adverse Events Leading to Discontinuation in a Placebo-Controlled, Double-Blind Trial With a 4-Week Dose Escalation Schedule.** Adverse Event followed by Placebo (N=286) first, 16 mg/day (N=279) second, 24 mg/day (N=273) third. **Nausea:** <1%, 2%, 4%; **Vomiting:** 0%, 1%, 3%; **Anorexia:** <1%, 1%, <1%; **Dizziness:** <1%, 2%, 1%; **Syncope:** 0%, 0%, 1%.

**Adverse Events Reported in Controlled Trials:** The reported adverse events in trials using RAZADYNE<sup>TM</sup> (galantamine hydrobromide) Tablets reflect experience gained under closely monitored conditions in a highly selected patient population. In actual practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior and the types of patients treated may differ. The majority of these adverse events occurred during the dose-escalation period. In those patients who experienced the most frequent adverse event, nausea, the median duration of the nausea was 5-7 days. Administration of RAZADYNE<sup>TM</sup> with food, the use of anti-emetic medication, and ensuring adequate fluid intake may reduce the impact of these events. The most frequent adverse events, defined as those occurring at a frequency of at least 5% and at least twice the rate on placebo with the recommended maintenance dose of either 16 or 24 mg/day of RAZADYNE<sup>TM</sup> under conditions of every 4-week dose-escalation for each dose increment of 8 mg/day, are shown in Table 2. These events were primarily gastrointestinal and tended to be less frequent with the 16 mg/day recommended initial maintenance dose.

**Table 2: The Most Frequent Adverse Events in the Placebo-Controlled Trial With Dose Escalation Every 4 Weeks Occurring in at Least 5% of Patients Receiving RAZADYNE<sup>TM</sup> and at Least Twice the Rate on Placebo.** Adverse Event followed by Placebo (N=286) first, RAZADYNE<sup>TM</sup> Dose (mg/day) 16 (N=279) second, 24 (N=273) third. **Nausea:** 5%, 13%, 17%; **Vomiting:** 1%, 6%, 10%; **Diarrhea:** 6%, 12%, 6%; **Anorexia:** 3%, 7%, 9%; **Weight decrease:** 1%, 5%, 5%.

**Table 3: The most common adverse events (adverse events occurring with an incidence of at least 2% with RAZADYNE<sup>TM</sup> treatment and in which the incidence was greater than with placebo treatment) are listed in Table 3 for four placebo-controlled trials for patients treated with 16 or 24 mg/day of RAZADYNE<sup>TM</sup>.**

**Table 3: Adverse Events Reported in at Least 2% of Patients With Alzheimer's Disease Administered RAZADYNE<sup>TM</sup> and at a Frequency Greater Than With Placebo: Body System/Adverse Event followed by Placebo (N=801) first, RAZADYNE<sup>TM</sup> (N=1040) second. **Body as a whole - general disorders:** Fatigue 3%, 5%; Syncope: 1%, 2%; **Central & peripheral nervous system disorders:** Dizziness 6%, 9%; Headache 5%, 8%; Tremor 2%, 3%; **Gastrointestinal system disorders:** Nausea 9%, 24%; Vomiting 4%, 13%; Diarrhea 7%, 9%; Abdominal pain 4%, 5%; Dyspepsia 2%, 5%; **Heart rate and rhythm disorders:** Bradycardia 1%, 2%; **Metabolic and nutritional disorders:** Weight decrease 2%, 7%; **Psychiatric disorders:** Anorexia 3%, 9%; Depression 5%, 7%; Insomnia 4%, 5%; Somnolence 3%, 4%; **Red blood cell disorders:** Anemia 2%, 3%; **Respiratory system disorders:** Rhinitis 3%, 4%; **Urinary system disorders:** Urinary tract infection 7%, 8%; Hematuria 2%, 3%. \*Adverse events in patients treated with 16 or 24 mg/day of RAZADYNE<sup>TM</sup> in four placebo-controlled trials are included.**

Adverse events occurring with an incidence of at least 2% in placebo-treated patients that was either equal to or greater than with RAZADYNE<sup>TM</sup> treatment were constipation, agitation, confusion, anxiety, hallucination, injury, back pain, peripheral edema, asthenia, chest pain, urinary incontinence, upper respiratory tract infection, bronchitis, coughing, hypertension, fall, and purpura. There were no important differences in adverse event rates related to dose or sex. There were too few non-Caucasian patients to assess the effects of race on adverse event rates. No clinically relevant abnormalities in laboratory values were observed. Other Adverse Events Observed During Clinical Trials: RAZADYNE<sup>TM</sup> Tablets were administered to 3055 patients with Alzheimer's disease. A total of 2357 patients received galantamine in placebo-controlled trials and 761 patients with Alzheimer's disease received galantamine for at least one year and approximately 200 patients received galantamine for two years. To establish the rate of adverse events, data from all patients receiving any dose of galantamine in 8 placebo-controlled trials and 6 open-label extension trials were pooled. The methodology to gather and codify these adverse events was standardized across trials, using WHO terminology. All adverse events occurring in approximately 0.1% are included, except for those already listed elsewhere in labeling, WHO terms too general to be informative, or events unlikely to be drug caused. Events are classified by body system and listed using the following definitions: frequent adverse events – those occurring in at least 1/100 patients; infrequent adverse events – those occurring in 1/100 to 1/1000 patients; rare adverse events – those occurring in 1/1000 to 1/10000 patients; very rare adverse events – those occurring in fewer than 1/10000 patients. These adverse events are not necessarily related to RAZADYNE<sup>TM</sup> treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies. **Body As a Whole – General Disorders:** Frequent: chest pain, asthenia, fever, malaise; **Cardiovascular System Disorders:** Infrequent: postural hypotension, hypotension, dependent edema, cardiac failure, myocardial ischemia or infarction; **Central & Peripheral Nervous System Disorders:** Infrequent: vertigo, hypertonia, convulsions, involuntary muscle contractions, paresthesia, ataxia, hypokinesia, hyperkinesia, apraxia, aphasia, leg cramps, tinnitus, transient ischemic attack or cerebrovascular accident; **Gastrointestinal System Disorders:** Frequent: flatulence; Infrequent: gastritis, melena, dysphagia, rectal hemorrhage, dry mouth, saliva increased, diverticulitis, gastroenteritis, hiccup; Rare: esophageal perforation; **Heart Rate & Rhythm Disorders:** Infrequent: AV block, palpitation, atrial arrhythmias including atrial fibrillation and supraventricular tachycardia, QT prolonged, bundle branch block, T-wave inversion, ventricular tachycardia; Rare: severe bradycardia; **Metabolic & Nutritional Disorders:** Infrequent: hyperglycemia, alkaline phosphatase increased; **Platelet, Bleeding & Clotting Disorders:** Infrequent: purpura, epistaxis, thrombocytopenia; **Psychiatric Disorders:** Infrequent: apathy, paranoia, paranoid reaction, libido increased, delirium; Rare: suicidal ideation; Very rare: suicide; **Urinary System Disorders:** Frequent: incontinence; Infrequent: hematuria, micturition frequency, cystitis, urinary retention, nocturia, renal calculi; **Post-Marketing Experience:** Other adverse events from post-approval controlled and uncontrolled clinical trials and post-marketing experience observed in patients treated with RAZADYNE<sup>TM</sup> include: **Body as a Whole – General Disorders:** dehydration (including rare, severe cases leading to renal insufficiency and renal failure). **Psychiatric Disorders:** aggression. **Gastrointestinal System Disorders:** upper and lower GI bleeding. **Metabolic & Nutritional Disorders:** hypokalemia. These adverse events may or may not be causally related to the drug.

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