New Mutation Linked to 6% of Familial Parkinson's

BY CHRISTINE KILGORE
Contributing Writer

Screening for a recently identified mutation shown to cause approximately 5%-6% of familial and 1%-2% of apparently sporadic cases of Parkinson's disease will likely become an important component of genetic testing and counseling for this disease, according to investigators involved in the research.

"No other single mutation identified so far … has occurred with such high frequency" in patients with Parkinson's disease, said William C. Nichols, Ph.D., of Cincinnati Children's Hospital Medical Center, and his associates. Their report was one of three on the mutation published online in the Lancet.

However, two issues need to be resolved before genetic testing for Parkinson's disease can fulfill its potential, Dr. Nichols told this newspaper. "First, there is nothing which can be done for patients carrying the genetic mutation and thus might be predisposed to developing Parkinson's disease. And …[w]e can't yet predict what an individual's chances of developing the disease are, given they carry a predisposing mutation."

The new research reported in The Lancet builds on findings published last year showing that mutations in the gene termed *LRRK2* (for leucine-rich repeat kinase 2) cause some forms of autosomal dominant Parkinson's disease (Neuron 2004;44:601-7). The gene codes for the protein dardarin, which is the first kinase to be implicated in the disease.

In research completed since then, a specific mutation in the *LRRK2* gene, Gly2019Ser, was identified in several families.

The investigators of the just-published studies sought to investigate the frequency of this mutation and its role in susceptibility to Parkinson's disease.

Dr. Nichols and his colleagues analyzed 358 North American families with at least one pair of siblings with Parkinson's disease.

They found that 35 of 767 affected members of these families (5%)—in 20 of the 358 families—had at least one copy of the mutated gene.

One of these 35 patients was homozygous for the mutation, they reported (The Lancet [online] http://image.thelancet.com/extras/04let12014web.pdf).

Alessio Di Fonzo, M.D., of the University of Milan, and his colleagues, also detected the mutation in 4 of 61 families (7%) with Parkinson's disease and apparent autosomal dominant inheritance. The families were from Italy, Portugal, and Brazil (The Lancet [online] http://image.thelancet.com/extras/04let12084web.pdf).

And William P. Gilks, of the Institute of Neurology and National Hospital for Neurology and Neurosurgery in London, and his associates, detected heterozygous Gly2019Ser mutations in 8 (2%) of 482 apparently sporadic cases, predominantly from the southeast of England.

The new research builds on data that mutations in the *LRRK2* gene cause some forms of autosomal dominant Parkinson's disease.

Three of the patients turned out to have positive family histories (two involved first-degree relatives, and one involved a second-degree relative), Mr. Gilks and his colleagues reported (The Lancet [online] http://image.thelancet.com/extras/04let12032web.pdf).

Each of the studies included large control populations; the mutation was absent from all of the control populations tested.

Alexis Brice, M.D., who commented on the studies in the same online issue of The Lancet, called identification of the Gly2019Ser mutation "a major advance."

The mutation "accounts for a surprisingly high proportion of both familial and isolated cases (of the disease)," he said in an editorial.

Still, there is much to learn, he said. Patients with the Gly2019Ser mutation have typical clinical features of Parkinson's disease, for instance, but the associated clinical spectrum "must be better established," he said.

Pathologic markers also must be better understood; the neuropathology in patients with the mutations—for instance, the extent and type of Lewy bodies—appears to vary considerably, even within the

Continued on following page

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Available in 4 mg, 8 mg, and 12 mg tablets and oral solution 4 mg/mL.

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BEFORE PRESCRIBING, PLEASE CONSULT COMPLETE PRESCRIBING INFORMATION OF WHICH THE FOLLOWING IS A BRIEF SUMMARY.

INDICATION
REMINYL® (galantamine hydrobromide) is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

CONTRAINDICATIONS
REMINYL® is contraindicated in patients with known hypersensitivity to galantamine hydrobromide or to any excipients used in the formulation.

WARNINGS
Anesthesia: Galantamine is likely to exaggerate the neuromuscular blocking effects of succinylcholine-type and similar neuromuscular blocking agents during anesthesia.
Cardiovascular Conditions: 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. 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. 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.
Gastrointestinal Conditions: 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). REMINYL® has been shown to produce nausea, vomiting, diarrhea, anorexia, and weight loss. (See **ADVERSE REACTIONS**)
Genitourinary : Cholinomimetics may cause bladder outflow obstruction.
Neurological Conditions: Seizures: Cholinesterase inhibitors are believed to have some potential to cause generalized convulsions. In clinical trials, there was no increase in the incidence of convulsions with REMINYL® compared to placebo.
Pulmonary Conditions: Galantamine should be prescribed with care to patients with a history of severe asthma or obstructive pulmonary disease.

PRECAUTIONS
Information for Patients and Caregivers: The recommended administration is twice per day, preferably with morning and evening meal. Dose increases should follow minimum of four weeks at prior dose. Following the recommended dosage and administration can minimize the most frequent adverse events associated with use of the drug. 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 REMINYL® 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 REMINYL® Oral Solution. Caregivers should direct questions about the administration of the solution to either their physician or pharmacist.
Special Populations
Hepatic Impairment: In patients with moderately impaired hepatic function, dose titration should proceed cautiously (See **CLINICAL PHARMACOLOGY** in full prescribing information and **DOSAGE AND ADMINISTRATION**). The use of REMINYL® 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** in full prescribing information and **DOSAGE AND ADMINISTRATION**). In patients with severely impaired renal function (CL_{cr} < 9 ml/min) the use of REMINYL® is not recommended.
Drug-Drug Interactions
Use with Anticholinergics: Galantamine 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 were the major enzymes involved in the metabolism of galantamine. CYP3A4 mediated the formation of galantamine-N-oxide, whereas CYP2D6 was involved in the formation of O-desmethyl-galantamine. *In vivo* - Cimetidine increased the bioavailability of galantamine by approximately 16%. Ranitidine had no effect on the PK of galantamine. Ketoconazole increased the AUC of galantamine by 30%. Erythromycin affected the AUC of galantamine minimally (10% increase). Paroxetine 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. *In vivo* - The protein binding of warfarin was unaffected by galantamine. Galantamine at 24 mg/day had no effect on the steady-state pharmacokinetics of digoxin (0.375 once daily) when they were coadministered. In this study, however, one healthy subject was hospitalized for 2nd and 3rd degree heart block and bradycardia.
Carcinogenesis, Mutagenesis and Impairment of Fertility: In a 24-month oral carcinogenicity study in rats, a trend for an increase in endometrial adenocarcinomas was observed at 10 mg/kg/day (4 times the Maximum Recommended Human Dose [MRHD] on a mg/m² basis or 6 times on an exposure [AUC] basis and 30 mg/kg/day (12 times MRHD on a mg/m² 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/m² 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/m² 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/m² 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/m² basis).
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/m² 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/m² basis) during the period of organogenesis. There are no adequate and well-controlled studies of REMINYL® (galantamine hydrobromide) in pregnant women. REMINYL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

PRECAUTIONS *(continued)*
Nursing Mothers: It is not known whether galantamine is excreted in human breast milk. REMINYL® 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 REMINYL® in children is not recommended.

ADVERSE REACTIONS
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 (nausea, vomiting and anorexia) the principle reason for discontinuing galantamine.
Adverse Events Reported in Controlled Trials: The majority of reported adverse events occurred during the dose-escalation period of the controlled trials. In those patients who experience the most frequent adverse event, nausea, the median duration of the nausea was 5 to 7 days.
Administration of REMINYL® 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, 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 REMINYL® under conditions of every 4 week dose-escalation, were primarily gastrointestinal and tended to be less frequent with the 16 mg/day recommended initial maintenance dose. They included nausea (5%, 13% and 17%), vomiting (1%, 6% and 10%), diarrhea (6%, 12% and 6%), anorexia (3%, 7% and 9%) and weight decrease (1%, 5% and 5%) for placebo, 16-mg/day and 24-mg/day treatment groups respectively.
The most common adverse events (adverse events occurring with an incidence of 2% with REMINYL® treatment and in which the incidence was greater than with placebo treatment) for patients in controlled trials who were treated with 16 or 24 mg/day of REMINYL® were: fatigue 5%, syncope 2%, dizziness 9%, headache 8%, tremor 3%, nausea 24%, vomiting 13%, diarrhea 9%, abdominal pain 5%, dyspepsia 5%, bradycardia 2%, weight decrease 7%, anorexia 9%, depression 7%, insomnia 5%, somnolence 4%, anemia 3%, rhinitis 4%, urinary tract infection 8% and hematuria 3%.
Adverse events occurring with an incidence of at least 2% in placebo-treated patients that was either equal to or greater than with REMINYL® 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: The incidence of all adverse events occurring in approximately 0.1% of the patients during clinical trials, except for those adverse events already listed elsewhere in labeling, are defined as: frequent adverse events - those occurring in at least 1/100 patients; infrequent adverse events - those occurring in 1/100 to 1/1000 patients; and rare adverse events - those occurring in fewer than 1/1000 patients. **Body As a Whole – General Disorders:** *Frequent:* chest pain; **Cardiovascular System Disorders:** *Infrequent:* postural hypotension, hypotension, dependent edema, cardiac failure; **Central & Peripheral Nervous System Disorders:** *Infrequent:* vertigo, hypertonia, convulsions, involuntary muscle contractions, paresthesia, ataxia, hypokinesia, hyperkinesia, apraxia, aphasia; **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 fibrillation, QT prolonged, bundle branch block, supraventricular tachycardia, T wave inversion, ventricular tachycardia; **Metabolic & Nutritional Disorders:** *Infrequent:* hyperglycemia, alkaline phosphatase increased; **Platelet, Bleeding & Clotting Disorders:** *Infrequent:* purpura, epistaxis, thrombocytopenia; **Psychiatric Disorders:** *Infrequent:* apathy, paroniria, paranoid reaction, libido increased, delirium; **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 REMINYL® include:
Body as a Whole – General Disorders: dehydration (including rare, severe cases leading to renal insufficiency and renal failure)
Central & Peripheral Nervous System 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.

OVERDOSAGE
Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug. As in any case of overdose, general supportive measures should be utilized. Signs and symptoms of significant overdosing of galantamine are predicted to be similar to those of overdosing of other cholinomimetics.
In a postmarketing report, one patient who had been taking 4 mg of galantamine daily for a week inadvertently ingested eight 4 mg tablets (32 mg total) on a single day. Subsequently, she developed bradycardia, QT prolongation, ventricular tachycardia and torsades de pointes accompanied by a brief loss of consciousness for which she required hospital treatment.

DOSAGE AND ADMINISTRATION
The dosage of REMINYL® shown to be effective in controlled clinical trials is 16-32 mg/day given as twice daily dosing. As the dose of 32 mg/day is less well tolerated than lower doses and does not provide increased effectiveness, the recommended dose range is 16-24 mg/day given in a BID regimen. The dose of 24 mg/day did not provide a statistically significant greater clinical benefit than 16 mg/day. It is possible, however, that a daily dose of 24 mg of REMINYL® might provide additional benefit for some patients. The recommended starting dose of REMINYL® is 4 mg twice a day (8 mg/day). The dose should be increased to the initial maintenance dose of 8 mg twice a day (16 mg/day) after a minimum of 4 weeks. A further increase to 12 mg twice a day (24 mg/day) should be attempted after a minimum of 4 weeks at 8 mg twice a day (16 mg/day). Dose increases should be based upon assessment of clinical benefit and tolerability of the previous dose. REMINYL® should be administered twice a day, preferably with morning and evening meals. 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.
Doses in Special Populations: Galantamine plasma concentrations may be increased in patients with moderate to severe hepatic impairment. In patients with moderately impaired hepatic function (Child-Pugh score of 7-9), the dose should generally not exceed 16 mg/day. The use of REMINYL® in patients with severe hepatic impairment (Child-Pugh score of 10-15) is not recommended. For patients with moderate renal impairment the dose should generally not exceed 16 mg/day. In patients with severe renal impairment (creatinine clearance <9 ml/min), the use of REMINYL® is not recommended.

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REMINYL® oral solution is manufactured by: Janssen Pharmaceutica N.V. Beerse, Belgium
REMINYL® tablets and oral solution are distributed by: Janssen Pharmaceutica Products, L.P. Titusville, NJ 08560

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same family, noted Dr. Brice of Université Pierre et Marie Curie in Paris (The Lancet [online] http://image.thelancet.com/extras/04cmt455web.pdf).

He and the study's investigators also cited the need to know more about the precise penetrance of the mutation before the new results are translated into practice.

In addition to Mr. Gilks' finding of the mutation in patients who did not have any family history of Parkinson's disease, Dr. Nichols found that "despite the apparent autosomal dominant effect (of the mutation)," only 13 (37%) of the siblings with a mutation reported having a parent with Parkinson's disease. Dr. Di Fonzo and his colleagues also identified some asymptomatic carriers—a finding that suggests penetrance was reduced or was age dependent.

Identifying the gene raises ethical questions about its use in testing, given the lack of preventive therapy once the patient has been diagnosed.

Dr. Nichols, moreover, pointed out that, in his study, carriers of the mutation also had clinical symptoms that were less severe, despite having had the disease for a longer time, which suggests that "the mutation is associated with slowed disease progression," he commented.

Despite the unanswered questions, now that the Gly2019Ser mutation has been identified, "there will be requests for presymptomatic testing by offspring of carriers," Dr. Brice said in his commentary.

This "raises ethical issues similar to those for Huntington's disease" since, without a preventive treatment, "testing offers no direct medical benefit," he said.

Dr. Nichols, in his remarks to this newspaper, noted: "I would not be surprised if there were not some company that will soon offer genetic testing for Parkinson's disease, maybe even at the prenatal level, because people are willing to pay for it."

Dr. Brice noted that identification of the gene and the mutation should lead to a better understanding of the pathologic mechanism underlying Parkinson's disease, which will "hopefully lead to new treatments," he said. The last page on the genetic basis of Parkinson's disease is yet to be written, and it promises to be very exciting. ■

Multiple-Procedure Approach Improves Cerebral Palsy

FAJARDO, P.R. — A "multiple simultaneous procedures" approach to surgical management of upper limb cerebral palsy improves function and lessens deformity, Bruce R. Johnstone, M.D., said at the annual meeting of the American Association for Hand Surgery.

The technique involves the release, lengthening, or paralysis of deforming spastic muscles, as well as tendon transfers and joint stabilizations.

It is used to help improve the patient's appearance and the patient's ability to perform tasks of daily living such as dressing and proper hygiene, said Dr. Johnstone of Royal Children's Hospital, Melbourne (Australia).

A phone survey of 48 patients (or their caretakers) who had the surgery between 1992 and 2001 for upper limb spasticity showed that 41 (85%) were satisfied with the outcomes and felt the surgery was worthwhile.

Based on the 0-8 point House scale, median function level increased significantly from 2 points before the surgery to 4 points after the surgery.

Based on a 0- to 4-point cosmesis scale that was created for the study, cosmesis increased significantly from a median of 1 point to 3 points.

Scores for patient hygiene and the ability to dress oneself also increased significantly, Dr. Johnstone said.

The findings may be useful in counseling patients and their caretakers about potential outcomes following surgery, he added.

—Sharon Worcester

VERBATIM

'Melatonin is really my first-line choice because it is easy to get over the counter and there are no side effects.'

Dr. Todd D. Rozen, on cluster headache prophylaxis, p. 29.