Imaging Duo Sharpens Tumor Diagnosis Accuracy

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NEW ORLEANS — The combination of magnetic resonance spectroscopy with magnetic resonance imaging significantly improved the pretherapeutic diagnostic accuracy for pediatric brain tumors, according to findings from a retrospective study.

In a review of 122 children with newly detected brain tumors, Dr. Mark S. Shiroishi compared imaging reports with histopathologic findings. He found that the correct diagnosis was made 63% of the time (38/60) with contrast-enhanced magnetic resonance imaging (MRI). When magnetic resonance spectroscopy (MRS) was combined with contrast-enhanced MRI, the accuracy rate increased to 87% (54/62). MRI led to a partially correct diagnosis in 10% of cases (6/60), a rate that fell to 5% (3/62) when MRS was added.

Importantly, 27% of tumors (16/60) were incorrectly diagnosed with MRI alone, compared with 8% of those (5/62) who also underwent MRS. The difference in diagnostic accuracy between the two groups was statistically significant (*P* less than .01), said Dr. Shiroishi, a neuroradiologist at Childrens Hospital Los Angeles.

MR spectroscopy is a noninvasive way of monitoring the biochemical components of normal and abnormal brain tissue in vivo. MRS uses the same principles as MRI, but in MRS, a plot representing the chemical make-up of a region (rather than an image) is generated. MRS has proved useful in imaging tumors, infarcts, and epileptic foci. "Spectroscopy allows us to readily distinguish … medulloblastomas, pilocytic astrocytomas, choroid plexus papillomas, and choroid plexus carcinomas," said Dr. Shiroishi when he presented his findings at the annual meeting of the American Society of Neuroradiology.

"There is still a gray zone overlapping between anaplastic and regular astrocytomas and ependymomas," he noted. ■

patient treated with REQUIP XL and also levodopa/carbidopa developed melanoma. Patients using REQUIP XL should be made aware of these results and undergo periodic dermatologic screening.

5.9 Retinal Pathology

Human: Because of observations made in albino rats (see below), ocular electroretinogram (ERG) assessments were conducted during a 2-year, double-blind, multicenter, flexible-dose, L-dopa controlled clinical study of immediate-release ropinirole in patients with Parkinson's disease. A total of 156 patients (78 on immediate-release ropinirole, mean dose 11.9 mg/day and 78 on L-dopa, mean dose 555.2 mg/day) were evaluated for evidence of retinal dysfunction through electroretinograms. There was no clinically meaningful difference between the treatment groups in retinal function over the duration of the study. Albino Rats: Retinal degeneration was observed in albino rats in the 2-year carcinogenicity study at all doses tested (equivalent to 0.6 to 20 times the maximum recommended human dose (MRHD) of 24 mg/day on a mg/m^2 basis), but was statistically significant at the highest dose (50 mg/kg/day). Retinal degeneration was not observed in pigmented rats after 3 months in a 2-year carcinogenicity study in albino mice, or in 1-year studies in monkeys or albino rats. The potential significance of this effect for humans has not been established, but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (e.g., disk shedding) may be involved.

5.10 Binding to Melanin

Ropinirole binds to melanin-containing tissues (i.e., eyes, skin) in pigmented rats. After a single dose, long-term retention of drug was demonstrated, with a half-life in the eye of 20 days.

6 ADVERSE REACTIONS

The following adverse reactions are described in more detail in the *Warnings and Precautions* section of the label:

- Falling asleep during activities of daily living (5.1)
- Syncope (5.2)
- Symptomatic hypotension, hypotension, postural/orthostatic hypotension (5.3)
- Elevation of blood pressure and changes in heart rate (5.4)
- Hallucination (5.5)
- Dyskinesia (5.6)
- Major psychotic disorders (5.7)
- Events with dopaminergic therapy (5.8)
- Retinal pathology (5.9)

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug (or of another development program of a different formulation of the same drug) and may not reflect the rates observed in practice.

During the premarketing development of REQUIP XL, patients with advanced Parkinson's disease received REQUIP XL or placebo as adjunctive therapy in 1 clinical trial. In a second trial, patients with early Parkinson's disease were treated with REQUIP XL or the immediate-release formulation of REQUIP without L-dopa. Advanced Parkinson's Disease (With L-dopa): The most commonly observed adverse reactions (≥5% and numerically greater than placebo) in the 24-week, double-blind, placebo-controlled trial for the treatment of advanced Parkinson's disease during treatment with REQUIP XL were, in order of decreasing incidence: dyskinesia, nausea, dizziness, hallucination, somnolence, abdominal pain/discomfort, and orthostatic hypotension.

Approximately 6% of 202 patients treated with REQUIP XL discontinued treatment due to adverse event(s) compared with 5% of 191 patients who received placebo. The adverse event most commonly causing discontinuation of treatment with REQUIP XL was hallucination (2%).

Listed below are adverse reactions that occurred with a frequency of at least 2% (and were numerically greater than placebo) in patients with advanced Parkinson's disease treated with REQUIP XL who participated in the 26-week, double-blind, placebo-controlled study. In this study, either REQUIP XL or placebo was used as an adjunct to L-dopa. Adverse reactions were generally mild or moderate in intensity.

Treatment-Emergent Adverse Reaction Incidence in a Double-Blind, Placebo-Controlled Trial in Advanced Stage Parkinson's Disease (With L-dopa) (Events ≥2% of Patients Treated with REQUIP XL and >% with Placebo), listed by body system with the incidence for REQUIP XL (n = 202) followed by placebo (n = 191):

Ear and labyrinth disorders: vertigo (4,2)**; Gastrointestinal disorders:** nausea (11,4), constipations (4,2), abdominal pain/discomfort (6,3), diarrhea (3,2), dry mouth (2, <1);**General disorders:** edema peripheral (4,1), **Injury, poisoning, and procedural complications**: fall* (2,1); **Musculoskeletal and connective tissue disorders:** back pain (3, 2); **Nervous system disorders:** dyskinesia* (13,3), dizziness (8,3), somnolence (7,4); **Psychiatric disorders:** hallucination (8,2), anxiety (2,1); **Vascular disorders:** orthostatic hypotension (5,1), hypotension (2,0), hypertension*(3,2). *dose related.

Although this study was not designed for optimally characterizing dose-related adverse reactions, there was a suggestion (based upon comparison of incidence of adverse reactions across dose ranges for REQUIP XL and placebo) that the incidence for dyskinesia, hypertension, and fall was dose-related to REQUIP XL.

The incidence for many adverse reactions with REQUIP XL treatment was increased relative to placebo (i.e., REQUIP XL % - Placebo % = treatment difference ≥2%) in either the titration or maintenance phases of the study. During the titration phase, an increased incidence (shown in descending order of % treatment difference) was observed for dyskinesia, nausea, abdominal pain/discomfort, orthostatic hypotension, dizziness, vertigo, hypertension, peripheral edema, and dry mouth. During the maintenance phase, an increased incidence was observed for dyskinesia, nausea, dizziness, hallucination, somnolence, fall, hypertension, abnormal dreams, constipation, chest pain, bronchitis, and nasopharyngitis. Some adverse reactions developing in the titration phase persisted (≥7 days) into the maintenance phase. These "persistent" adverse reactions included dyskinesia, hallucination, orthostatic hypotension, and dry mouth.

The incidence of adverse reactions was not clearly different between women and men. Early Parkinson's Disease (Without L-dopa): The most commonly observed adverse reactions (≥5%) in the 36-week early Parkinson's disease trial during treatment with REQUIP XL were, in order of decreasing incidence: nausea (19%), somnolence (11%), abdominal pain/discomfort (7%), dizziness (6%), headache (6%), and constipation (5%). The type of adverse reactions and the frequency (i.e. incidence) with which they occurred were generally similar over the whole treatment period in this study of early Parkinson's disease patients who were initially treated with REQUIP XL or the immediate-release formulation of REQUIP and subsequently crossed over to treatment with the other formulation.

During the titration phase, an increased incidence with REQUIP XL compared with the immediate-release formulation of REQUIP (i.e., REQUIP XL % - REQUIP IR % = treatment difference ≥2%), shown in descending order of % treatment difference, was observed for: constipation, hallucination, vertigo, abdominal pain/discomfort, nausea, vomiting, fall, headache, diarrhea, pyrexia, and flatulence. During the maintenance phase, an increased incidence was observed for fall, myalgia, and sleep disorder. Several adverse reactions developing in the titration phase persisted (≥7 days) into the maintenance phase. These "persistent" adverse reactions included: constipation, hallucination, muscle spasms, flatulence, insomnia, sleep disorder, abdominal pain/discomfort, cough, and nasopharyngitis.

6.2 Adverse Reactions Observed During the Clinical Development of the Immediate-Release Formulation of REQUIP for Parkinson's Disease (Advanced and Early).

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 trials of another drug (or of another development program of a different formulation of the same drug) and may not reflect the rates observed in practice.

In patients with advanced Parkinson's disease who were treated with the immediate-release formulation of REQUIP, the most common adverse reactions (≥5% treatment difference from placebo; presented in order of decreasing treatment difference frequency) were dyskinesia (21%), somnolence (12%), nausea (12%), dizziness (10%), confusion (7%), hallucinations (6%), headache (5%), and increased sweating (5%). In patients with early Parkinson's disease who were treated with the immediate-release formulation of REQUIP, the most common adverse reactions (≥5% treatment difference from placebo; presented in order of decreasing treatment difference frequency) were nausea (38%), somnolence (34%), dizziness (18%), syncope (11%), viral infection (8%), fatigue (7%), leg edema (6%), asthenia (5%), and dyspepsia (5%).

7 DRUG INTERACTIONS

7.1 P450 Interaction

In vitro metabolism studies showed that CYP1A2 is the major enzyme responsible for the metabolism of ropinirole. There is thus the potential for inducers or inhibitors of this enzyme to alter the clearance of ropinirole. Therefore, if therapy with a drug known to be a potent inducer or inhibitor of CYP1A2 is stopped or started during treatment with ropinirole, adjustment of the dose of ropinirole may be required.

Coadministration of ciprofloxacin, an inhibitor of CYP1A2, with immediate-release ropinirole increased the AUC of ropinirole by 84% on average and C_{max} by 60% *[see Clinical Pharmacology (12.3) of the full prescribing information]*.

Cigarette smoking is expected to increase the clearance of ropinirole since CYP1A2 is known to be induced by smoking. In one study in patients with Restless Legs Syndrome, cigarette smokers had an approximate 30% lower C_{max} and a 38% lower AUC than did nonsmokers, when those parameters were normalized for dose.

There is no evidence of interaction between ropinirole and other CYP1A2 substrates (e.g., theophylline).

Ropinirole and its circulating metabolites do not inhibit or induce P450 enzymes therefore ropinirole is unlikely to affect the pharmacokinetics of other drugs by a P450 mechanism *[see Clinical Pharmacology (12.3) of the full prescribing information]*.

7.2 L-dopa

Coadministration of carbidopa + L-dopa (SINEMET®*) with immediate-release ropinirole had no effect on the steady-state pharmacokinetics of ropinirole. Oral administration of immediate-release ropinirole increased mean steady-state C_{max} of L-dopa by 20%, but its AUC was unaffected *[see Clinical Pharmacology (12.3) of the full prescribing information]*.

7.3 Estrogens

Population pharmacokinetic analysis revealed that higher doses of estrogens (usually associated with hormone replacement therapy [HRT]) reduced the oral clearance of ropinirole by approximately 35%. Dosage adjustment is not needed for initiating REQUIP XL in patients on estrogen therapy because patients are individually titrated with REQUIP XL to tolerance or adequate effect. If estrogen therapy is stopped or started during treatment with REQUIP XL, then adjustment of the dose of REQUIP XL may be required.

7.4 Dopamine Antagonists

Since ropinirole is a dopamine agonist, it is possible that dopamine antagonists such as neuroleptics (e.g., phenothiazines, butyrophenones, thioxanthenes) or metoclopramide may diminish the effectiveness of REQUIP XL. Patients with a history or presence of major psychotic disorders should be treated with dopamine agonists only if the potential benefits outweigh the risks.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies using ropinirole in pregnant women. REQUIP XL should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

In animal reproduction studies, ropinirole has been shown to have adverse effects on embryo-fetal development, including teratogenic effects. Treatment of pregnant rats with ropinirole during organogenesis resulted in decreased fetal body weight, increased fetal death, and digital malformations at 24, 36, and 60 times the MRHD, respectively. The combined administration of ropinirole at 8 times the MRHD and a clinically relevant dose of L-dopa to pregnant rabbits during organogenesis produced a greater incidence and severity of fetal malformations (primarily digit defects) than were seen in the offspring of rabbits treated with L-dopa alone. In a perinatal-postnatal study in rats, impaired growth and development of nursing offspring