Echo Monitoring May Be Indicated

Valve Damage *from page 1*

dose of either pergolide or cabergoline and the severity of valve regurgitation, according to Dr. Renzo Zanettini and associates in the cardiac rehabilitation unit and Parkinson Institute of the Istituti Clinici di Perfezionamento, Milan.

"Our findings confirm safety concerns related to the use of pergolide and show that an increased risk of cardiac valvulopathy also exists in patients taking cabergoline," the authors concluded.

In the U.S., pergolide carries an FDA warning of possible cardiac valvulopathy and fibrotic complications that discourages its use in patients with a history of valvular heart disease and recommends a baseline cardiovascular evaluation and periodic echocardiograms.

Cabergoline has been the subject of case reports and one case-control study from Japan (Neurology 2006;67:1225-9), suggesting an association with valvulopathy.

Dr. Zanettini and colleagues noted the presence of increased mitral tenting, a geometric measure of the position of the leaflets that can be an early indicator of valvular dysfunction, in patients receiving ergot-derived dopamine agonists such as pergolide and cabergoline. Patients receiving non–ergot-derived dopamine agonists also had increased mitral tenting.

Although the latter patients did not have evidence of elevated rates of frank regurgitation, this finding "suggests that follow-up echocardiographic monitoring is advisable in all patients with Parkinson's disease who are treated with dopamine agonists," they wrote (N. Engl. J. Med. 2007;356:39-46).

The second study, a nested case-control study drawn from the United Kingdom General Practice Research Database, calculated incidence rates of newly diagnosed cardiac valve regurgitation in 11,417 patients who had received prescriptions for antiparkinsonian medications.

Cardiac valve regurgitation rates were elevated with current use of pergolide (adjusted incidence-rate ratio 7.1; 95% confidence interval 2.3 to 22.3) and cabergoline (adjusted incidence rate ratio 4.9; 95% confidence interval 1.5 to 15.6), but not with current use of any other dopamine agonist.

In what investigators termed an "unexpected" finding, concurrent use of amantadine also had a significant association with regurgitation (adjusted incidence rate ratio 3.5 (95% confidence interval 1.1 to 11.3), although they said the role of this antiviral/antidyskinetic medication "requires further investigation."

Daily doses of greater than 3 mg of either pergolide or cabergoline, or the use of either drug for 6 months or more, conferred a "particularly elevated" adjusted incidence-rate ratio, reported Dr. René Schade of the department of clinical pharmacology, Charité-Universitätsmedizin, Berlin (N. Engl. J. Med. 2007;356:29-38).

In both New England Journal of Medicine studies, valvular abnormalities in patients taking pergolide or cabergoline were seen in the mitral, aortic, and tricuspid valves. Pergolide and cabergoline are potent agonists of 5-hydroxytryptamine$_{2B}$ (5-HT$_{2B}$) serotonin receptors, unlike dopamine agonists that were not associated with elevated cardiac valve disease in the study. They share this mechanistic pathway with fenfluramine and dexfenfluramine, antiobesity drugs withdrawn from the market in 1997 due to reports of valvular heart disease and pulmonary hypertension in patients taking the so-called "fen-phen" combination.

"Clearly, practitioners should avoid prescribing drugs that are potent 5-HT$_{2B}$-receptor agonists—a growing list of medications that now includes ergot derivatives (ergotamine, methysergide, and dihydroergotamine), dopamine agonists (pergolide and cabergoline), and amphetamine derivatives (fenfluramine and methylenedioxymethamphetamine [MDMA, or "ecstasy"])," Dr. Bryan L. Roth wrote in an accompanying editorial (N. Engl. J. Med. 2007;356:6-9).

Amantadine, which was associated with an elevated risk of valvular heart disease in the Berlin study, should be investigated to see whether it activates 5-HT$_{2B}$ receptors, said Dr. Roth, whose research group at the University of North Carolina, Chapel Hill, has been instrumental in unraveling the molecular mechanisms underlying valvulopathic drugs.

In the editorial, he and his colleagues "urged pharmaceutical companies and regulatory agencies to screen candidate drugs and their major metabolites at 5-HT$_{2B}$ receptors" before initiating clinical trials of new drugs "to prevent "fen-phen"-type disasters."

In the meantime, "I recommend that physicians do not prescribe medications with 5-HT$_{2B}$ agonist activity," he said in an interview.

Dr. Griffin called the journal studies "a little worrying," since they affirm what had been postulated to be a class effect of drugs that act as agonists at the 5-HT2B receptor.

Increased mitral tenting, an early indicator of valvular dysfunction, was seen in patients taking ergot-derived and non–ergot-derived DA agents.

Patients exposed to pergolide and cabergoline have echocardiograms, said Dr. Griffin, noting more information is needed before he would call for a moratorium on their use.

Less troubling is evidence in one study of tenting in patients exposed to other dopamine agonists, he said. While they may prove to be partial agonists of the 5-HT2b receptor, other anti-Parkinsonian drugs do not appear to have the same potential impact on the valves as pergolide and cabergoline, he said.

Neurologist Dr. Irene Litvan, Raymond Lee Lebby Professor of Parkinson Disease Research at the University of Louisville (Ky.) and director of the movement disorder program there, said in an interview that these articles confirm the importance of not using 5HT2b agonists in general. Neurologists have other options for treating Parkinson's.

"Ropinirole and pramipexole are excellent DA [dopamine agonists] and recently approved inhibitors of MAO-B have expanded our armamentarium," she said.

Further studies are needed to assess the risk of a valvulopathy when using amantadine, Dr. Litvan said.

"These findings will have little impact in my practice. Due to the risks of retroperitoneal and pleural fibrosis I have tended not to use ergot derived DA and following the 2004 reported risk of a fibrotic valvulopathy secondary to pergolide I discontinued the use of pergolide in patients who were referred to me who were on this drug. There are no appropriately powered head-to-head studies that evaluate if there are differences between ergot and non–ergot derived DA, but in practice non–ergot derived DA are as good as ergot-derived DA. I had difficulty switching pergolide to a non–ergot derived DA in a small number of patients and only one preferred to remain on this drug despite the warnings. Routine echocardiograms seem indicated for patients who opt to continue to be treated with DA that are 5HT2b agonists," she said.

Pergolide, marketed in the United States as Permax, is manufactured by Valeant Pharmaceuticals International. Cabergoline, marketed as Dostinex, is manufactured by Pfizer Inc. Valeant no longer promotes the product, but still makes it available for those who prescribe it.

FDA has approved Pfizer's revised label for Dostinex (cabergoline) (www.fda.gov). The new labeling includes: "As with other ergot derivatives, pleural effusion/pulmonary fibrosis and valvulopathy have been reported following long-term administration of cabergoline."

The Milan study was supported by the Italian Parkinson Association, the Grigioni Foundation for Parkinson's Disease, and Istituti Clinici di Perfezionamento. Investigators disclosed support from GlaxoSmithKline, Pfizer, Boehringer Ingelheim, and Novartis. The Berlin-based study, which included investigators from Berlin and McGill University Health Centre in Montreal, was supported by Schering, GlaxoSmithKline, Boehringer Ingelheim, Astra-Zeneca, Novartis, and Organon. ■

Frequency, Pain of Restless Legs Should Guide Therapy

BY JOHN R. BELL
Associate Editor

BALTIMORE — When deciding which drug to prescribe for a patient with restless legs syndrome, the frequency and painfulness of symptoms are crucial to making the correct choice, Dr. Christopher J. Earley said at a neurology meeting sponsored by Johns Hopkins University.

"For [75%]-80%, depending on the population that you deal with, pain is not what they experience," said Dr. Earley, a neurologist at Johns Hopkins. A far greater portion instead describe their RLS as uncomfortable, he said. But for those with painful RLS, that pain must be treated. "So I tend to use the antiseizure medications [e.g., gabapentin, lamotrigine, pregabalin] or the opiates as my first line of treatment, as opposed to the dopamine [DA] agents, when I'm dealing with painful symptoms," he said. If it's partially responsive ... then I will consider the dopamine agonists. If I really get desperate ... I might consider sedation."

For painless nightly RLS, he advises a DA agonist as first-line therapy, opiates as a second-line choice, and sedatives as third-line treatment. Frequent painless RLS (2-3 nights per week) warrants a sedative first, followed by opiates and, if those fail, levodopa. For occasional RLS (less than twice per week), he advises either a half or whole tablet of carbidopa 25 mg/levodopa 100 mg (available as Sinemet and Parcopa brands) as needed for first-line therapy. "This is going to be effective in 99.9% of patients, barring side effects like nausea," he said.

He recommends a DA agonist and a sedative as second- and third-line treatment, respectively. Drugs that can aggravate RLS include neuroleptics and antiemetics, as well as SSRIs and tricyclic antidepressants (except for bupropion and trazodone) and antihistamines.

A disadvantage of the DA agonists is that they take 2 hours to reach peak dose effect (3 hours if taken with a meal or after symptom onset), compared with 30-60 minutes for opiates. Thus dopamine agonists are most useful for situations such as airplane flights, he said, but less practical for nighttime RLS. Dr. Earley favors levodopa for occasional nonpainful RLS. "If you have any doubts about whether this is RLS or not RLS, you can use the levodopa"-carbidopa combination (carbidopa 25 mg/levodopa 100 mg) of half to 1 ½ tablets for 3 days. "If they get no real benefits from that, this is not RLS—at least not the RLS that I know."

The DA agonists do have other disadvantages besides their delayed effect, Dr. Earley noted. They can cause compulsive behaviors. They also can cause hypersomnia. "It's almost like narcolepsy," he said. Moreover, DA agonists risk the phenomenon of augmentation, whereby an increase in dosage leads to an increase in symptoms, so that a patient is treated effectively for a time period in which RLS occurs (e.g., bedtime), but then the RLS begins to occur either before or after the treated period. "Augmentation is the single biggest reason why you have to stop this drug." He advised that when patients taking a DA agonist for sleep complain of RLS symptoms before or after bedtime, the physician should not prescribe additional drugs.

Notably, opiates do not pose augmentation risk, he said. With opiates, "you're going to get about 85% of them up walking away relatively happy."

Iron deficiency has been implicated as a possible cause of RLS, he noted. "I check ferritins in everybody," he said. ■