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Article

Calcium Channel Blockers Reduce Parkinson Disease Risk

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ARTICLE IN BRIEF

In an analysis of prospective data, subjects prescribed centrally acting calcium channel blockers were 27 percent less likely to develop Parkinson disease compared to those who did not receive the drugs.

Use of common calcium channel blockers for hypertension appears to reduce the risk of Parkinson disease (PD), according to a new epidemiologic study published online ahead of print in the *Annals of Neurology*. The finding reinforces preclinical results showing that such drugs protect dopamine neurons from a variety of toxic insults.

Study leader Beate Ritz, MD, professor of epidemiology at the School of Public Health of the University of California-Los Angeles, said she was inspired by a preclinical study to investigate whether there was any evidence these drugs exerted an effect in humans.

Figure. DR. BEATE RI...
Image Tools

The drugs in question include isradipine, nimodipine, and nifedipine, among others. All are dihydropyridine derivatives, which block so-called L-type calcium channels on smooth muscle, reducing the force of contraction and thus reducing blood pressure.

L-type calcium channels are also found in the CNS, particularly in dopamine neurons, and those drugs that cross the blood-brain barrier also block these central channels. In the preclinical work, that blockade appeared to be critical to the protective effect of the drugs.

To explore the potential effects in humans, Dr. Ritz used records in the national hospital and outpatient database from Denmark, identifying all incident PD cases from 2001 to 2006. She found almost 2,000 PD patients, and matched them with almost 10,000 controls. For each, she

examined prescription records to identify treatment with antihypertensives between 1995, when the database was begun, up to two years before the PD diagnosis.

Unlike in previous studies of antihypertensives and PD, the Danish database provided information not just on the class of drug, but also the specific drug used for each person in the study. This was important, Dr. Ritz explained, because one commonly prescribed calcium channel blocker, amlodipine, doesn't readily cross the blood-brain barrier, and would thus not be expected to exert a central effect.

She found that subjects prescribed centrally acting calcium channel blockers were 27 percent less likely to develop PD compared to those who did not receive the drugs. The effect had an odds ratio of 0.73, with a 95 percent confidence interval between 0.53 and 0.97.

The protective effect was not seen for amlodipine, nor for antihypertensives with other mechanisms of action. “To me, that's very remarkable,” Dr. Ritz said.

She found no confounding factors in the literature to suggest that patients with incipient PD might be preferentially prescribed amlodipine versus a different calcium channel blocker, strengthening the case that the brain-penetrant drugs were exerting a true protective effect.

“As an observational epidemiologist, you like to be very careful with what you are saying, but I was really struck by the specificity of what we were seeing with these calcium channel blockers,” Dr. Ritz said.

There was no effect seen for smoking, a well-accepted protective factor for PD. Dr. Ritz noted that while smoking might increase hypertension and therefore treatment with antihypertensives, there is no reason to think that smokers requiring treatment would preferentially receive brain-penetrant calcium channel blockers.

There was no correlation between risk and either duration or intensity of drug exposure, she noted. “I am not sure what that means, but it may just be we don't have enough data. We need to watch that as we go forward.”

Dr. Ritz is now examining the next three years of data from the same database, identifying new PD patients and looking in more detail at the question of total drug exposure. She also hopes to look at the effect of these drugs in other populations.

“I think it's very encouraging that there might be some potentially protective effect with drugs that are already in human use, that have few side effects, and are available generically,” she said.

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EXPERT COMMENTARY

D. James Surmeier, PhD, who was the senior author on a 2007 paper in *Nature* showing protective effects of calcium channel blockers in animal models, said he was “very excited” about Dr. Ritz's results.

“We hypothesized that calcium entry into dopaminergic neurons could be a basic factor in Parkinson disease, based on toxin models,” said Dr. Surmeier, the Nathan Smith Davis Professor and Chair of the Department of Physiology at the Feinberg School of Medicine at Northwestern University and director of the Morris K. Udall Research Center of Research Excellence for Parkinson's Disease at Northwestern University. “The problem is that toxin models have had relatively little predictive validity to this point, so there is no substitute for experience in humans.”

He noted that Claudia Becker, PhD, and colleagues reported in a 2008 *Neurology* paper that calcium channel blockers were potentially protective based on analysis of data on PD patients in a UK research database The earlier study did not separate amlodipine, the most commonly prescribed member of the class, from the other members, potentially diluting the strength of the effect.

Dr. Surmeier pointed out that Dr. Ritz's analysis was based on a larger data set.

Figure. DR. D. JAMES...
Image Tools

“The fact that Dr. Ritz showed that the effect was restricted to those that crossed the blood-brain barrier, and not the other dihydropyridines, which had the same peripheral effect, is encouraging from a therapeutics development standpoint.”

“Having epidemiological data of this particular sort gives us good reason to think we ought to go ahead with a clinical trial in early stage PD,” Dr. Surmeier said. A small trial is currently underway to test safety of isradipine in PD patients, at the request of the FDA, before proceeding to a larger efficacy trial. Encouragingly, the drugs have few if any side effects in non-PD patients.

A key question is whether the drugs can be protective in patients already diagnosed with PD. (Dr. Ritz's study was restricted to treatment initiated up to two years before diagnosis). “We don't know whether it's too late at that point,” Dr. Ritz said. “Even if it turns out that treatment at that stage is not preventive, it doesn't mean that drugs given earlier wouldn't be protective.”

Currently, Dr. Surmeier said, the only strong candidates for earlier treatment are those people with disease-causing mutations. However, he said, since age is the number one risk factor for PD, and since the drugs are safe and inexpensive, one could contemplate more widespread prophylactic treatment, “a little like a baby aspirin.”

Dr. Surmeier noted that advances in his own work have shifted his thoughts on how the calcium channel blockers are exerting their effects. In his original paper, reported in *Nature* in 2007, high concentrations of isradipine caused the neurons to upregulate a juvenile ion channel, which he concluded might be central to the protective effect. Since then, however, he has shown that low concentrations, similar to those expected in the human brain at approved doses, are also protective, without upregulating the juvenile ion channel.

"At lower doses, you stop the calcium channel, which is the bad thing that stresses the cell, but the cell never slows down, never misses a beat," Dr. Surmeier said. The danger of overactive calcium channels likely involves mitochondria, he added. Calcium influx requires a rapid response and resulting high metabolic demand. Over the course of 50 years, "the mitochondria just wear out."

But can the cell survive without functioning calcium channels? Apparently it can. Dopamine neurons fire in two modes, Dr. Surmeier explained: tonically, to maintain an ambient level of dopamine in target structures like the striatum; and in bursts, in response to rewarding events, to induce changes that underlie motor learning.

Tonic firing "is absolutely critical for brain function," he said, while burst firing — a function of calcium channels — is not. Completely ablating the channel leads to no obvious changes in learning. "Astonishingly, the calcium channels are not required for function," Dr. Surmeier said.•

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