Two advances in the management of Parkinson disease

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ABSTRACT

Levodopa should generally be avoided early in the course of Parkinson disease; dopamine agonists, particularly second-generation agents such as ropinirole (Requip) and pramipexole (Mirapex), carry a smaller long-term risk of dyskinesia and should be used instead. Deep brain stimulation is remarkably effective in refractory cases and may well usher in a new era in the treatment of chronic neurologic disease.

TWO ADVANCES should help patients with Parkinson disease, but at different stages: second-generation dopamine agonists for patients in the beginning stages of the disease, and electrical deep brain stimulation for patients for whom drugs have become ineffective.

Primary care physicians will need to assume more of the care of parkinsonian patients in coming years, for two reasons. First, the number of patients with Parkinson disease is expected to increase, from the current 1.5 million to nearly 4 million by 2015 as the baby-boom generation enters the age of greatest risk. At the same time, there will be relatively fewer movement disorder specialists.

Primary care physicians will especially be seeing patients in the early stages of Parkinson disease. And the "opening game" matters: we now have compelling evidence that the initial treatment decisions have a great impact on long-term disability.

WHAT'S WRONG WITH LEVODOPA?

Levodopa was the first rationally derived neurologic drug: patients with Parkinson disease were found to lack dopamine, and levodopa, a precursor of dopamine that can cross the blood-brain barrier, was designed to replace it. At the time, it was a miracle drug, allowing patients who had been bedridden to resume nearly normal activities of daily living.

In Parkinson disease, the 'opening game' matters

Unfortunately, after 4 or 5 years of levodopa use, many patients develop significant and often severe complications, including dyskinesia (abnormal involuntary movements) and motor fluctuations, often resulting in unpredictable periods of increased disability. These side effects can be more disabling than the parkinsonian symptoms themselves.

And they are common: nearly one third of patients develop dyskinesia after 4 or 5 years of therapy (quite severe in half), and about 25% develop motor fluctuations. Reducing the levodopa dose often relieves dyskinesia, but at the expense of motor function. Combining levodopa with carbidopa permits lower doses of levodopa to be used and reduces side effects in the body, but not neurologic side effects.

Until recently, this concern was somewhat academic because many patients had no viable options to levodopa therapy. First-gen-

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Ropinirole produces less dyskinesia than levodopa

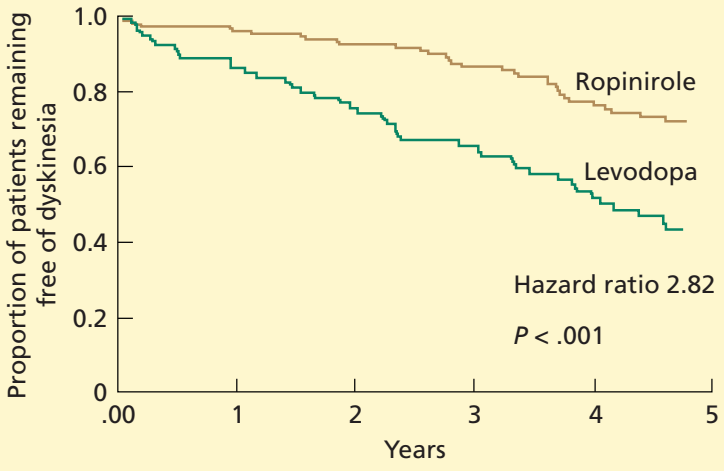

FIGURE 1. Proportion of patients remaining free of dyskinesia in a randomized trial of ropinirole and levodopa in Parkinson disease.

FROM RASCOL O, BROOKS DJ, KORCZYN AD, DE DEYN PP, CLARKE CE, LANG AE. A FIVE-YEAR STUDY OF THE INCIDENCE OF DYSKINESIA IN PATIENTS WITH EARLY PARKINSON'S DISEASE WHO WERE TREATED WITH ROPINIROLE OR LEVODOPA. 056 STUDY GROUP. N ENGL J MED 2000; 342:1484–1491.

eration dopamine agonists such as bromocriptine (Parlodel) and pergolide (Permax) also cause significant side effects and are ergot alkaloids and so must be used with caution in patients with cardiovascular disease. Anticholinergic drugs must be used with caution in patients who are elderly or are cognitively impaired.

SECOND-GENERATION DOPAMINE AGONISTS

Within the last 5 years, however, a new generation of dopamine agonists has been introduced, including ropinirole (Requip) and pramipexole (Mirapex). Compared with older dopamine agonists, the newer drugs cause fewer side effects, and they are not ergot alkaloids and so have fewer contraindications.

Randomized trials of dopamine agonists

Both ropinirole[1] and pramipexole[2] were compared with levodopa-carbidopa for early Parkinson disease in large, randomized, double-blind trials. Physicians were allowed to titrate the dose of the study medication, and if it did not relieve symptoms sufficiently, the physician was allowed to supplement the study medication with open-label levodopa-carbidopa. In both studies, the primary end point was the development of dyskinesia within a 5-year follow-up.

Results. Both studies demonstrated nearly identical results. Patients in the ropinirole and pramipexole groups had a much lower risk for developing dyskinesia than the levodopa-carbidopa groups, even if they required supplemental levodopa-carbidopa (FIGURE 1).

These two studies suggest that early use of dopamine agonists can change the natural history of levodopa-treated Parkinson disease. This suggestion was supported by two subsequent studies examining the effect of dopamine agonists vs levodopa on survival of dopaminergic neurons in patients with Parkinson disease, as measured by positron emission tomography[3] and single-photon emission computed tomography.[4]

STARTING THERAPY: WHETHER AND WHAT

At the outset, the physician should consider whether the patient's symptoms are severe enough to warrant therapy with drugs that can cause side effects and must be taken long-term.

If the answer is yes, the next question is which agent to use. This depends on the patient's age and whether he or she has comorbid cardiovascular or cognitive conditions.

For young patients (< 65 years) without comorbid conditions, I would recommend the physician use whichever dopaminergic agonist he or she has experience using, and preferably one that is less expensive. The reason is that physicians generally do best using medications they have the most experience with. In younger patients without cognitive or cardiovascular problems, any of the dopamine agonists are generally well tolerated.

For patients 65 years and older, I would recommend a second-generation dopamine agonist. Ropinirole appears to be the best tolerated, followed by pramipexole.

Deep brain stimulation for Parkinson disease

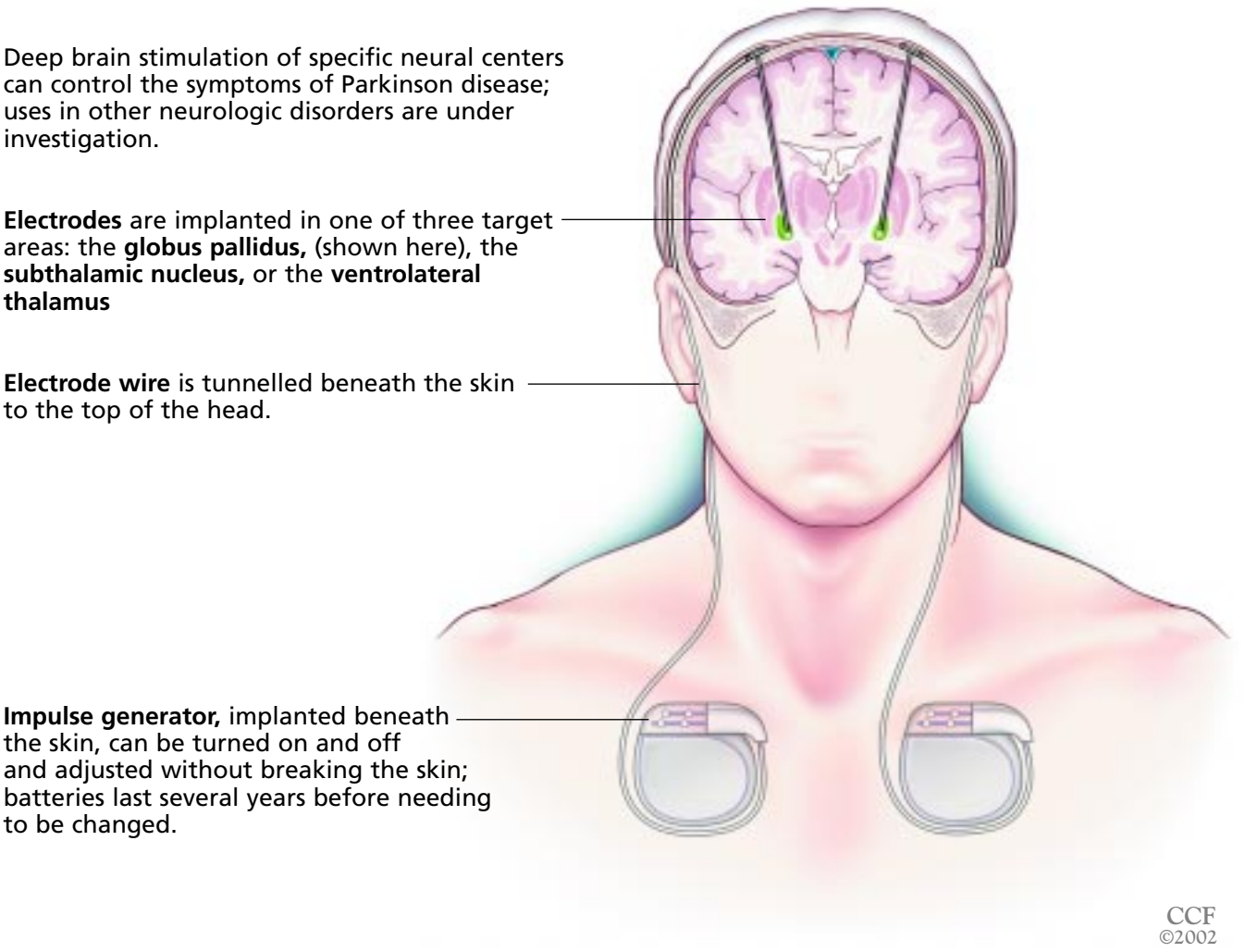

FIGURE 2

For patients with cardiovascular comorbid conditions, I would use one of the second-generation (non-ergot alkaloid) dopamine agonists. Pramipexole is easier to use because of ease of dose titration; however, ropinirole is better tolerated.

For patients with cognitive comorbid conditions, I would use ropinirole because it has a lower risk of cognitive side effects.

A common mistake is to use inadequate doses. These drugs are started at low doses and titrated upward according to symptoms. In the study of ropinirole by Rascol and colleagues,[1] the mean daily dose after titration was about 10 mg, and was increased to 16.5 mg by the 5th year of therapy.

Sleep attacks and antiparkinsonian drugs

Recently there have been reports of significant and sudden sedation in patients taking dopamine agonists,[5] some of whom have fallen asleep at the wheel while driving. This problem can happen with any of the dopamine agonists—first-generation and second-generation—and also with levodopa-carbidopa.

Patients should be advised of this possibility. When starting a patient on one of these agents or when increasing the dose, we often suggest that that patients start on a weekend and temporarily refrain from activities, such as driving a car, in which they would endanger themselves and others if they were to suddenly become sedated. However, even patients who have been on a stable regimen still may experience sleepiness when taking the medications.

Is not clear to what degree these problems are exacerbations of daytime drowsiness in patients already at high risk for sleep disturbances, or if they represent "sleep attacks" that can occur without warning or in the setting of

known daytime drowsiness. Patients with sleep disturbances should be considered at increased risk and be appropriately advised.

DEEP BRAIN STIMULATION: BETTER LIVING THROUGH ELECTRICITY

An exciting new treatment for refractory Parkinson disease is to implant electrodes to stimulate precise locations in the brain. Called *deep brain stimulation*, this therapy opens a new avenue of treatment not only for Parkinson disease but for other conditions as well. (See our website, "Deep brain stimulation for Parkinson's disease: Is it right for your patient?" at **http://www.clevelandclinicmeded.com/deepbrain2/deepbrainhome.htm.**)

Technique

The targets are small and located deep in the brain. To reach them with precision, we must use stereotactic surgical techniques.

On the morning of surgery, we attach a metal halo or frame around the patient's head. Four pins hold the frame rigidly to the skull, which is anesthetized in advance with local anesthetic. The patient then undergoes magnetic resonance imaging (MRI) and computed tomography (CT).

Deep brain stimulation can double 'on time' without dyskinesia

Internal landmarks localizing the target and seen on the MRI and CT scans are spatially correlated with the external metal frame. The coordinates of the internal landmarks are translated to coordinates on the metal frame, which guide placement of the electrodes.

Even so, MRI and CT scans do not have sufficient spatial resolution. Many times, the exact target cannot be visualized but is approximated by its spatial relation to a line connecting the anterior and posterior commissures.

To find the precise target, the unique and distinct electrophysiologic properties of neurons in the target are used. Before placement of the permanent stimulating lead, microelectrodes are used to record the electrical extracellular action potentials. Once these are found, the microelectrode is placed by the permanent therapeutic lead.

Usually, two electrodes are placed through burr holes in the skull, one on the left and one on the right. Each lead is connected by an extension wire to an impulse generator, which is a specifically modified cardiac pacemaker implanted beneath the skin of the chest below the clavicle.

The impulse generator can be controlled by radiofrequency transmissions from a briefcase-sized programming unit. The patient receives a small handheld unit with which he or she can turn the impulse generators on and off.

The electrode has four metal contacts at its tip. Any combination of contacts can be used for stimulation. In addition, the frequency, polarity, voltage, and pulse width can be individually programmed. This provides for the great deal of flexibility needed to tailor the therapy to each individual patient and to adjust the stimulation as the patient's condition changes.

Targets for deep brain stimulation

There are three potential targets for deep brain stimulation in Parkinson disease: the ventrolateral thalamus, the globus pallidus internal segment, and the subthalamic nucleus (FIGURE 2).

The ventrolateral thalamus is rarely used because it is effective only for tremor and rigidity. Even if a patient is bothered only by tremor or rigidity, it is virtually inevitable that he or she will develop other symptoms of Parkinson disease that will not respond to thalamic deep brain stimulation.

On the other hand, deep brain stimulation of the globus pallidus internal segment and subthalamic nucleus is highly effective and relatively safe. Our general practice is to recommend subthalamic nucleus stimulation because it is the only target that, when stimulated, allows patients to substantially reduce their medications, and it is the easiest to perform technically.

Studies of deep brain simulation

Several randomized studies have documented the safety and efficacy of deep brain simulation.

How does one conduct a randomized, double-blind trial of a therapy that involves implanting electrodes in the brain? In some studies, the evaluators were blinded to the therapy, and the patients were crossed over

from stimulation to no stimulation without their knowledge. Another strategy is to use ineffective stimulation parameters without the patient's knowledge.

The studies strongly indicate that the efficacy demonstrated in larger open-label clinical trials is an effect of deep brain stimulation and not a placebo effect.

The largest study[6] included 134 patients who received either subthalamic or globus pallidus deep brain stimulation, which was turned off and on without the patients' knowledge in a crossover fashion. The primary outcome measure was the Unified Parkinson Disease Rating Scale motor examination, which demonstrated a 51% reduction or improvement ($P < .001$) with stimulation of the subthalamic nucleus and 33% ($P < .001$) with stimulation of the globus pallidus in the off-medication state.

Improvement was seen across nearly all symptom categories, and improvement over baseline scores was statistically significant, with the exception of gait and postural stability in patients receiving globus pallidus deep brain stimulation.

A more telling statistic is the increase in the "on time" without dyskinesia with deep brain stimulation. Parkinson patients cycle through three states:

- "Off time," in which the patient is experiencing parkinsonian symptoms
- On time with dyskinesia, in which the parkinsonian symptoms are relieved but the patient experiences significant or disabling dyskinesia
- On time without dyskinesia—"quality time" for patients.

Both globus pallidus and subthalamic nucleus deep brain stimulation resulted in a doubling of on time without dyskinesia. In contrast, the newly introduced medication entacapone (Comtan) increased the on time without dyskinesia by much less.

The therapeutic efficacy is even more striking when one realizes that these patients had end-stage disease and often could not obtain sufficient symptomatic control even under the care of experienced movement disorder specialists.

EXPERIMENTAL USES OF DEEP BRAIN STIMULATION

Deep brain stimulation has proven remarkably effective in the treatment of Parkinson disease, and is considered standard and accepted medical therapy for essential tremor, dystonia, and tremor due to cerebellar lesions such as in multiple sclerosis.

Clinical trials are underway for a variety of neurologic and psychiatric conditions including epilepsy, depression, and obsessive-compulsive disorder. Other trials are planned for treatment of patients in a minimally conscious state due to severe head injury.

As we gain better understanding of the pathophysiology of neurologic disorders and of the mechanisms of action of deep brain stimulation, we should be able to provide more effective therapy to patients with a wider range of diseases.

Some may be surprised at the efficacy of deep brain stimulation. However, the brain is basically an electrical device that receives, processes, and transmits information electronically. Neurotransmitters, which have been the basis for pharmacologic therapy, are just the messengers—they are not the message. The brain has more in common with a computer than with a stew of chemicals. Thus, there is good reason to believe that we are on the verge of a new era in therapeutics.

The brain has more in common with a computer than with a stew of chemicals

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