CASE REPORT

Fibrotic complications induced by ergot derivatives dopamine agonists – time to change treatment guidelines for Parkinson's disease?

Roth J., Ulmanová O., Růžička E.
Movement Disorder Center, Department of Neurology, 1st Medical Faculty, Charles University, Prague, Czech Republic

SUMMARY

Ergot derivative dopamine agonists such as pergolide, bromocriptine and dihydroergocriptine, used in treatment of Parkinson's disease, can cause pleural, pericardial, retroperitoneal and valvular fibrotic changes. Case No. 1: A 56-year-old woman with PD was treated with pergolide 3 mg/24 h starting July 2002. In June 2003 edema of lower extremities was firstly noticed and echocardiography found a minor mitral regurgitation without any morphological changes of the valve. In January 2004 left- sided cardiac failure rapidly developed and echocardiography revealed multivalvular insufficiency with predominating severe mitral regurgitation. Mitral valve replacement was performed and pergolide was changed to ropinirole. To date neither cardiac functions nor motor status have adequately compensated. Case No. 2: A 66-year-old-man with PD since 1996 was treated with pergolide 3 mg/day starting 1999. In the beginning of 2004 leg edema appeared. On examination bilateral hydronephrosis with ureteric strictures and incipient renal insufficiency was found. Bilateral ureteroplasty was performed, and the histology showed periureteric fibrosis. Treatment with steroids was initiated, and pergolide was changed to pramipexole. Despite the treatment, the fibrosis progressed, requiring ureteral stenting. Based on a review of the literature and our own experience, we propose the following guidelines to minimize the risk of complications:
A. Do not use EDA as first-line dopamine agonists. B. Perform regular follow-ups of all patients treated with EDA, especially monitoring the major symptoms: dyspnoea, cough, fatigue, leg edema (also asymmetric), symptoms of urinary outflow obstruction, cardiac insufficiency, chest pain, heart murmur. An elevated ESR, C-reactive protein or anaemia support the diagnosis. C. Have all symptomatic patients undergo workup for serosal fibrosis (according to type of complication): chest X-ray or CT scan, spirometry, renal functions, renal ultrasound, CT of retroperitoneum. D. Before the introduction of EDA therapy, examine the renal functions, perform chest X-ray and echocardiography. Screening echocardiography should be performed at 3–6 months and subsequently in every 6–12 months.
Key words: Parkinson's disease, fibrosis, ergot derivatives, pergolide.

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Parkinson's disease (PD) develops in consequence of excessive extinction of dopaminergic neurons of pars compacta substantiae nigrae in mesencephalon. Lack of dopamine is the cause of principle signs of PD, i.e. akinesia, rigidity and tremor. Substitution of missing dopamine is the base of treatment with L-3,4-dihydroxyphenylalanine (L-DOPA) and dopamine agonists.

Dopamine agonists (DA) are compounds with powerful direct agonist effect on dopamine receptors in striatum; this is the reason for their therapeutical use both in early and in late stage of PD. In the early stage of the disease their use is justified not only by symptomatic effect on motor manifestations of disease but also by postponed onset of late complications of PD in comparison with L-DOPA administration since the beginning of the disease. Combined therapy with DA and L-DOPA is the treatment of late motor complications of PD.

Classification of DA is based on their chemical structure: the drugs derived from ergot alkaloids are called ergoline or ergot alkaloids (EDA) as compared to non-ergoline derivatives, i.e. derivatives with different chemical structure.

In addition to PD, DA are also used for the treatment of restless legs syndrome and in endocrinology, especially for the treatment of prolactinoma. Some other antimigraine drugs are derived from EDA: e.g. ergotamine, dihydroergotamine, methylsergide. The main representatives of EDA are: pergolide (in Czech Republic registered as Permax, Hizest), bromocriptine (Medocriptine, Serocryptine, Parlodel), lisuride (not registered in this country), terguride (Mysalfon), dihydroergocriptine (Almirid) and carbegolide (not registered for PD in this country).

Adverse reactions such as fibrotic organ-based changes, mainly in retroperitoneal space and in pleuropulmonary and pericardial regions, have occurred sporadically with most of these products. The first adverse effect of the treatment was noted as early as 1966 in patients with headache treated with methylsergide (1). In patients with PD, fibrotic retroperitoneal, pleuropulmonary and pericardial complications were noted later, with the use of bromocriptine (2-6) and pergolide (7, 8). Pericardial and pleuropulmonary fibrotization has been detected recently with the use of cabergoline (9). These complications have been considered very rare so far and have not

Assoc. Professor Jan Roth, MD
Department of Neurology, 1st Medical Faculty
Charles University
Kateřinská 30
120 21 Prague 2
Czech Republic
E-mail: roth@beba.cesnet.cz

been taken into consideration to any significant extent in day-to-day neurological practice.

In recent years during the treatment with these drugs, mainly with pergolide (one of the most often used DA), fibrotic changes of tricuspid, mitral and aortic valves have also been detected, leading to significant regurgitation and in some patients to sudden death or immediate threat to life (10-16).

Some reports bring warning data about prevalence of valvular disorders in patients with PD treated with pergolide. Van Camp (13) studied 78 patients with PD treated with pergolide and found on transthoracic echocardiography restrictive valvular heart disease in 26 subjects (33%).

Considerably advanced damage was found in 15 out of all patients (19%). The tricuspid valve was very often affected. The study shows that dominating impairment of the tricuspid valve in conjunction with normal width of ventricular wall and along with absence of calcifications on echocardiogram, reflects possible drug-induced damage or the presence of carcinoid (see below). As opposed to the findings in older people with different origin of valvular disorders, e. g. with degenerative or inflammatory affection, the tricuspid valve remains relatively undamaged and calcifications are often present.

According to information of the producer of Permax (Eli Lilly), there were 94 reports of valvulopathy worldwide up to September 15, 2004, and 84 out of them were assessed as probably caused by pergolide; 32 other cases were reported during postmarketing studies and in the literature review. About 1,700,000 patients have been treated with the product so far (17).

The mechanism responsible for the development of fibrotisation remains unclear. In the past, idiosyncratic immune response of predisposed organism to the external trigger – a drug - was suspected.

Recently it has been suggested that the causative relation lies in the serotonine system and the serotonergic effects of these drugs. The key role is probably played by 5-HT_{2B} type of receptors, whose activation leads to stimulation of fibroblasts and to induction of fibrous tissue production (14, 18). For example, these receptors are also present in heart musculature. The serotonin hypothesis is also supported by the fact that very similar fibrotic valvular changes also occur in carcinoid (hyperproduction of serotonin) and during the treatment with central anorectics fenfluramine and its derivatives (serotonergic effect) (19-21). According to some trials, the fibrotic complications are probably not dependent on the duration of treatment and on the dosage of inducing drugs. Clinical symptoms caused by fibrotic complications have been noted after several months of pergolide application and also after many years (13).

So far, the origin of fibrotic complications has been considered to be directly connected with the structure of ergot alkaloids (15). Experience with non-ergot DA – pramixenol (Mirapexin) and ropinirole (Requip) – is far less comprehensive at present, and therefore the possibility that adverse reactions also appear with these drugs cannot be ruled out. For example, it is known that bromocriptine and pergolide may cause torpid swellings of the lower limbs. Similar swellings may appear in some patients treated with pramixenole or ropinirole. Even though in these cases fibrotic changes have not been proved, a related mechanism of the swellings cannot be ruled out (22). A very recent report (23) has really proved the occurrence of valvular disorders also in patients with PD treated with ropinirole.

Withdrawal of the inducing drug may lead to regression of fibrotic changes, but this is not always the case. Excessive fibrotisation can be favorably influenced by long-term treatment with corticosteroids (15).

The following two case reports may exemplify the severity of organ-based fibrotic complications.

CASE REPORT NO. 1

A 56-year-old female treated for PD since 2001 with selegiline and biperidene. Pergolide was given at a daily dose of 3 x 1 mg starting July 2002. In 2000, after a mild ischaemic stroke, echocardiography showed normal function of the left ventricle without dilatation, hypertrophy and with insignificant degenerative changes on mitral valve. In June 2003 swellings of the lower parts of the calves appeared; repeated echocardiography indicated minor mitral regurgitation with morphologically intact findings on the valve. In January 2004 rapidly worsening dyspnoea and vast edemas of the lower extremities developed over several days. Left-sided heart insufficiency was diagnosed and multiple valvular changes with dominating mitral regurgitation, aortic and tricuspid regurgitation were detected on echocardiography; they were assessed as medium-severe.

In the past history there were no data about either previous rheumatic fever or treatment with fenfluramine derivatives. The patient did not suffer from ischaemic heart disease. In April 2004 mitral valve replacement was performed. In the postoperative period, pergolide was changed to ropinirole at a dose of 3 x 6 mg. Since motor function was not entirely satisfactory, L-DOPA at a dose 3 x 50 mg was added after several weeks. To date neither cardiac functions nor motor status have been adequately compensated.

CASE REPORT NO. 2

A 66-year-old male with Parkinson's disease since 1996 has been treated with L-DOPA from the very beginning. In 1999 pergolide at a daily dose of 1.5 mg was added, increased to 3 mg/24 hrs in 2000. Early in 2004 livid leg edemas appeared. On examination, bilateral hydronephrosis with ureteric strictures and incipient renal insufficiency were found. Bilateral ureteroplasty was performed, and histology showed periureteral fibrosis. Treatment with corticosteroids was initiated after the operation, and pergolide was changed to pramipexole. Patient's motor function was stabilized, but despite the corticosteroids treatment hydronephrosis developed again and the patient was indicated for ureteral stent implantation due to persisting stenosis.

DISCUSSION

Our present experience with the therapeutical effects of pergolide and other EDA confirms their importance for therapy of the early and late stages of PD (24). Up to the spring 2004 no occurrence of serious organ-based complications had been observed in our study population. It is possible that subclinical changes were overlooked and the possibility of fibrotic complications was not taken into consideration. The case of the patient with multiple valvular disorders shows that pergolide may induce fibrotic changes of severe degree even if it is administered in medium therapeutical dosage over only 22 months (cumulative dose about 2 g). In fact, no long-term treatment with high dose pergolide is necessary for creation of fibrotic complications.

In that patient first echocardiography was performed at a time when she was not taking any pergolide. Minor mitral regurgitation with no apparent pathological changes of the valves is unlikely to have been responsible for the sudden worsening of the condition within the next three years of the patient's life, if it were not for an inducing factor – pergolide. Unfortunately, histological examination of the resected tissue was not performed, therefore the relation of treatment and EDA could not be convincingly confirmed.

Table 1. Symptoms of organ-based fibrotic complications

PLEUROPULMONARY FIBROSIS
Dyspnoea
Cough
Chest pain
Weight loss or weight gain
Fatigue syndrome
RETROPERITONEAL FIBROSIS
Swellings of the lower limbs (also asymmetrical)
Problems with micturition
Weight gain (liquid retention)
Fatigue syndrome
PERICARDIAL AND VALVULAR FIBROSIS
Development of heart insufficience
Chest pain
Weight loss or weight gain
Dyspnoea
Heart murmur
Fatigue syndrome

Table 2. Examination methods appropriate for diagnosis of fibrotic complication

PLEUROPULMONARY FIBROSIS
Spirometry
Chest X-ray
Chest CT
Non-specific: anaemia, higher ESR, acute-phase proteins
RETROPERITONEAL FIBROSIS
Examination of renal functions
Renal ultrasound
CT of retroperitoneum
Non-specific: anaemia, higher ESR, acute-phase proteins
PERICARDIAL AND VALVULAR FIBROSIS
Echocardiography
Non-specific: anaemia, higher ESR, acute- phase proteins

In our male patient with retroperitoneal fibrosis it seems that there is no possible explanation for fibrotic changes other than the influence of pergolide. In this patient the fibrotising process was confirmed by histological examination of the sample of the resected tissue.

It is very important to realize that even mild edemas of the lower limbs or other non-specificic symptoms (Tab. 1) in patients with PD treated with EDA may signal the onset of fibrotic complications. It is necessary to screen such patients and follow them (Tab. 2). If any suspicion of fibrotic complications arises, it is usually necessary to continue treatment with DA, because in most cases there is a risk of serious worsening of the condition in the patients with PD. Change of EDA to other non-ergot drugs seems to be an obvious step to prevent further deterioration.

CONCLUSION AND PROPOSALS FOR MEASURES

Today DA are an indispensable part of symptomatic therapy of PD, representing the first line treatment together with L-DOPA.

Our current state of knowledge leads us to change our attitude towards EDA in the treatment of PD:

1. EDA as the first choice treatment are not recommended. As with monotherapy and in combined treatment of PD, DAs of non-ergot type, i. e. pramipexole and ropinirole, should by preferred.

2. If ropinirole or pramipexole fails (intolerance of the drug, drowsiness, unsatisfactory motor effect in usual therapeutical doses), EDA can be used as the second choice treatment. It is strictly forbidden to use EDA when tissue fibrosis or valvulopathy is present in past medical history.

3. Always before initiation of EDA therapy it is necessary to explain possible risks to patients and to perform examination of kidney functions, chest X-ray and echocardiography in an attempt to detect preexisting abnormalities. It is recommended to repeat echocardiography after 3 – 6 months, and the next echocardiographic check-ups should be performed during 6 – 12 months. If valvulopathy is diagnosed, it is necessary to interrupt the treatment immediately. When using pergolide, its daily dose should not exceed 5 mg.

4. Recently it has not been considered correct to interrupt ergot derivatives in patients with PD who are benefiting from the therapy and who do not show clinical signs of complications. Nevertheless, these patients should be regularly followed up (see item 3).

Note

In November 2004 pergolide supplier (Eli Lilly Czech Republic) sent a letter to Czech doctors, informing them of the changes in SPC (Summary of Product Characteristic) for Permax owing to the increased number of reported cases of valvulopathy related to the usage of the product. The changes were discussed and approved by the State Institute for Drug Control (Státní ústav pro kontrolu léčiv). The measures recommended by the producer are in accordance with our above-mentioned recommendations.

Abbreviations

DA - dopamine agonists
EDA - ergot dopamine agonists
L-DOPA - L-dihydroxyphenylalanine
PD - Parkinson´s disease
SPC - Summary of Product Characteristic

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