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

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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/24h 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 multiple valvular 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.

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, metylergide. 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 metylergide (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
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 (Elly 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 the inducing factor – pergolide. Unfortunately, histological examination of the resected tissue was not performed, therefore the cause and the possibility of fibrotic complications was not taken into consideration. The case of the patient with multiple valvular disorders in our study showed that pergolide may induce fibrotic changes of the tricuspid, mitral and aortic valves have also been detected, leading to significant regurgitation, aortic and tricuspid regurgitation were detected on echocardiography; they were assessed as medium-severe.

The following two case reports may exemplify the severity of the 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%).

CASE REPORT NO. 1

A 56-year-old female treated for PD since 2001 with selegiline and biperiden. Pergolide was given at a daily dose of 3 x 1 mg for the first time in 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 2004 three clefts of the mitral valve were found; 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, pericarditis 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 was given 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 ureterolysis 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 therapeutic 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 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.
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-specific 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 benefitting 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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