Summary HTA

german agency for HTA of
German Institute of Medical
Documentation and Information

HTA-Report | Summary

DAHTA@DIMDI
Waisenhausgasse 36-38a
D-50676 Köln

Tel.: +49 221 4724-525
Fax: +49 221 4724-444
dahta@dimdi.de
www.dimdi.de

The treatment of Parkinson's disease with dopamine agonists

Konta B, Frank W

Health political background

Parkinson's disease is a chronic neurodegenerative disease which frequency increases whose causes are unknown and whose therapies partly are connected to a clear reduction of the quality of life. This disease is well known in the society. Patients are easily recognized and in the case of no adequate therapy they suffer of social isolation. Illnesses within the age of active working are not rare.
Miscellaneous therapy approaches which considerably show different effects, side effects as well as costs exist. Each patient has to be considered individually, but the decision for a treatment is an evaluation of a more cost intensive therapy, improve of quality of life and a possible delay for severe stages for the disease.
There is the political question, whether the need for additional financial expenditure can be compensated by a delay of the disease, reduced hospital costs of costs for nursing.
What can a health politician do to improve the problem of these patients? Is it just to pay more for the patients? Is there a general social advantage which can be achieved?
From the scientific point of view there are many hints that the dopamine agonists – the more expensive class of substances is worth to be paid because reductions of costs in the field of long-term-care or an early stop of working can be postponed.
These facts should be brought to a detailed health economic evaluation since these individual indications from international studies are not transferable directly to the German health system with such a certainty, which is necessary for real political decisions.

Introduction

Parkinson's disease is a chronic degenerative organic disease which cause is unknown. A disappearance of cells with melanin in the substantia nigra is considered as biological artefact of the disease, which causes a degenerative loss of neurons in the corpus striatum of mesencephalon. This structure produces also the transmitter substance dopamine. Due to this disappearance of cells dopamine is not produced in a sufficient quantity which is needed for movement of the body.
The clinical symptoms of Parkinson's disease is mainly the bradykinesis, tremor (especially one-sided in rest), and rigor (muscles tends to resistance at passive movement), and occurs when 50 to 60% of the cells disappeared and the lack of dopamine is about 80 %.
This HTA-report will evaluate the effectiveness of dopamine agonists for the treatment of Parkinson's disease.

All HTA reports are available for free of charge as full texts in the DAHTA database (only in German) and at German Medical Science (gms).

Within the scope of the

Bundesministerium
für Gesundheit

Questions

Dopamine agonists are used regularly for Parkinson's disease. This report tries to answer the following questions:

- What about the effectiveness and safety of dopamine agonists with the treatment of Parkinson's disease?
- What is the cost-efficiency of the therapy with dopamine agonists in comparison to other therapies?
- Are there ethical considerations important when this therapy is used?
- Which recommendations can be given for the German health care system for the use of dopamine agonists?

Methods

A systematic literature search was done in all relevant literature databases. The identified literature was examined by two independent reviewers and analysed for this report. The method for information synthesis should be quantified as much as possible which was difficult due to the bad direct comparison of the studies and the frequent lack of quality of the studies in the sense of evidence based medicine. Therefore qualitative methods of information synthesis were used.

Background of the disease

About 250,000 people suffer on Parkinson's disease in Germany. Another 100,000 can be assumed as not detected. Up to 180 patients per 100,000 habitants are estimated. About 1 % of the 60-years old people and 3 % of the 80-years old people have Parkinson's disease. 10 % of the patients are younger than 40 years, 30 % younger than 50 years. 40 % get the disease between 50 and 60 years. Men have a double risk to get the disease then women. Incidence is increasing with age.

The clinical symptoms or Morbus Parkinson is mainly the bradykinesis, tremor (especially one-sided in rest), and rigor (muscles goes in resistance to passive move, when 50 to 60 % of the cells disappeared and the lack of dopamine is about 80 %).

Diagnostic methods

An important method for the evaluation of the functionality is the UPDRS (Unified Parkinson's Disease Rating Scale) especially the part II "Activities of daily living", which comprehend an evaluation of the most important activities of a person, like talking, swallowing, writing, cutting food, practibility, hygiene, turn in bed, falling, walking, tremor and recognition.

Some procedures are necessary for testing the loss of dopamine neurons in the nigrostratial region. That is the PET (positron emission tomography) which needs the 6-florotopa marker.

An alternative method is SPECT (Single Photon emission tomography). The representation is done with the use of the ligand 123J-IPT or 123J-Beta-CIT, which can bind dopamine receptors. Postsynaptic dopamine receptos can be detected by 123J-IBZM. The loss of nerve ending in the corpus stratium can be detected by 123I-FP-CIT by a reduced density of dopamine-transporting proteins.

Dopamine agonists for treatment of Parkinson´s disease

Levodopa – the gold standard in the treatment of Morbus Parkinson
Since the introduction in the 1960´s L-Dopa (levodopa) is considered as the most effective therapy of Parkinson's disease, which reduces all cardinal symptoms and which is improved since then. At the beginning pure levodopa was used with doses of 300 to 400 mg per day to achieve a good therapeutic success. This led to side severe and frequent effects, because the major part of the substance is converted in the gastro intestinal tract to dopamine and other catecholamines.
The first improvement was the application of additional L-Dopa decarboxylasis inhibitors, which reduced the peripheral conversion and can not pass the blood-brain-barrier to lower the side effects. Nowadays L-Dopa-therapy is always combined with decarboxylasion inhibitors and/or COMT-inhibitors.
The deterioration continues due to the proceeding process in the substantia nigra which can not be influenced. The long-term-side effects – motorial complications – are the known problem of L-Dopa-Therapy. These are the motorial late-complication, like dyskinesia, hyperkinesias or akinesia. Especially akinesia which appears with the highest possible dose after a long-term-treatment (End-of-dose akinesia) a combination between intake of L-Dopa and motion can be seen.

Other antiparkinson substances

All other pharmaceuticals which are used for the treatment of Parkinson's disease can be classified into two classes - those substances which have an effect for the dopaminergal system and those with an effect for the basal ganglion cells.
The class of medication which effects the basal ganglion cells is the older one, modify the ganglion cells of the motoric system and show a lower effect. These are the class of anticholinergica and the NMDA-antagonists.
The huge class of dopaminerg substances are levodopa, monoaminoxidase-inhibitors (MAO-B-inhibitors), COMT-inhibitors and dopamine agonists.

Dopamine agonists

In practice dopamine agonists play an important role in the therapy of Parkinson's disease, because the corresponding receptors are targeted directly. Most of the pharmaceuticals develop the effect directly at the D2-receptors, whereas the role of different types of receptors is still unknown. All dopamine agonists have a direct effect to the dopamine receptors; they differ in respect to half-life and special effects to different subtypes of dopamine receptors (D1, D2, D3). The latest dopamine agonists have advantages because of the long half-life, which improves the sense of a continuous postsynaptic activation of the receptors.
A mono therapy of Parkinson's disease is possible with dopamine agonists and is used in early stages. In the course of time doses need to be increased with following side effects. Mono therapies are used especially with younger patients (before 40) due to early and severe L-Dopa-dyskinesia.
Clinical practice has shown that an add-on-therapy with dopamine agonists can reduce the dose of
L-dopa or can reduce dyskinesia. Basically this is possible with all the dopamine agonists; the selection of the specific substance is due to the individual patient and the tolerance.
Older dopamine agonists are ergotic dopamine agonists (derived from ergotic-alkaloids), later substances are not ergotic anymore and do not have an ergotic-alkaloid structure.

Dopamine agonists with ergotic structure

Ergotic dopamine agonists are alpha-dihydroergocriptine (DHEC), bromocriptine, lisuride, cabergoline, pergolide.
Studies to the effectiveness of ergotic dopamine agonists are studies for the initial therapy, mono therapy and add-on-therapy. Theses studies are not comparable to each other. Basically these show a good effectiveness of dopamine agonists against dyskinesia and significant differences are proven. The effectiveness of dopamine agonists is weaker then this of ledodopa, although the use of initial therapy at the beginning of the disease can postpone the use of levodopa or can reduce its dose for a longer period.
For Bromocriptine there are ten-years-studies for mortality. Life tables were used for comparison. There are no differences between bromocriptine and levodopa in respect to mortality.
The side effects of this group of dopamine agonists are nausea and vomiting, further dizziness and hypersomnia. A publication from 2004 showed a suspicious increased incidence of valvulopathy under treatment with pergolide.

Dopamine agonists with non-ergotic structure

These later non-ergotic dopamine agonists are ropinirole, pramipexole, rotigotine and piribedile.
Studies for non-ergotic dopamine agonists show as well as ergotic substances a good effect against dyskinesia. These medications can be used at the beginning of a disease to postpone the use of levodopa or to reduce the dose of levodopa in case of an add-on-therapy.
Similar to ergotic dopamine agonists the first direct effects against the symptoms of Parkinson disease are weaker then with levodopa, but significant better then with placebo. The latest dopamine agonist rotigotine was developed for transdermal use as tape and is active over a period of 24 hours.
Non-ergotic dopamine agonist studies with imaging were done and under ropinirol the progressive loss of stratial F-Dopa measurement could be postponed. Another study with pramipexol could show that the beta-CIT-parameters could be reduced.
Pharmacoeconomic studies show that the cost-benefit ratio is about US $ 20,000. This incremental cost-effectiveness ratio as well the costs per QALY is under the US-average.
The side effects are less frequent than with ergotic dopamine agonists and also not so severe.

Apomorphine

The dopamine agonist apomorphine is one of the oldest used medications out of this group. It has a special position, because the treatment is done by bolus injections or infusion.
Two very qualitative good studies could be found. The first one reports a quick effect of this injection, but the effect does not last as long as L-dopa. The second one reports a significant improvement of the UPDRS-Score and the daily periods of “off-time” in comparison to placebo. This medication is used for emergency treatment.
The side effects are comparable with other dopamine agonists. There are nausea, vomiting, hypersomnia as well as psychiatric disorders (confusion, hallucination).

Comparisons of the effect of dopamine agonists

In a review the later dopamine agonists ropinirol, pramipexol and pergolide were compared to the older substance bromocriptin. The newer substances show a better effectiveness, the differences can not be interpreted due to a lack of direct comparability.
An unsystematic review compares the effectiveness of different dopamine agonists as add-on-therapy with levodopa. No difference could be found between the oral dopamine agonists.

Comparisons of dopamine agonists with other antiparkinsonian treatment

Some studies were done for comparison of COMT-inhibitors, MAO-B-inhibitors and dopamine agonists. A meta analysis included seven studies. The results show, that all dopamine agonists could reduce the L-dopa dose significantly.
One publication showed a comparable effectiveness of MAO-B-inhibitor tolcapone and dopamine agonist pergolide in respect to the UPDRS-Score and the PDQ. Only the scale quality of life of the PDQ the MAO-inhibitor tolcapone was superior to the dopamine agonist pergolide. The porgolide group had a higher incidence of side effects.

Costs of dopamine agonists

When the prices are compared dopamine agonists are the most expensive ones for Parkinson treatment. The authors of the relevant studies conclude, that due to the cost-benefit-ratios it is seen, that the higher cost for dopamine agonists can be compensated by other costs. The increased costs for medication can be compensated by reduced costs especially costs for inpatient care or postponed need for long term care.

Ethical considerations

From ethic view the reduced quality of life has to be considered. Therefore an effective and long lasting improvement of symptoms is primary focused. L-Dopa is still the gold standard although the late complications are known.
Side effects are a big issue in the studies. Many studies demonstrate high rates of drop-out due to not tolerable side effects. There are no differences of the profile of side effects to levodopa. The dopamine agonists have comparable profiles, but some reported problems appear as more severe (e.g. vulvopathies under use of pergolid).
Dopamine agonists demonstrate that they do not deteriorate quality of life generally in comparison to other kinds of treatment.

Discussion

The strategy of treatment is depending of some factors. Recommendations of many experts show, that the treatment must be planned individually. Age at the beginning of therapy is very important. For younger patients (under 65 years) the risk for development of motoric fluctuations is much higher and therefore it is tried to use levodopa only at later stages of the disease.
The treatment of symptoms with levodopa and an additional decarboxyl-inhibitor is still the gold standard. Dopamine agonists have a fix place for the treatment of motoric fluctuations and dyskinesia, which are the late complications of a treatment with levodopa.

Dopamine agonists show a weaker effectiveness in comparison to levodopa. The positive effect of dopamine agonists are the late complications of levodopa. Early treatment with dopamine agonists can lower the increasing dose of levodopa or can postpone the use of levodopa.
Dopamine agonists could show significant improvement of symptoms of Parkinson disease in RCT. The advantage is especially for early stages of the disease an avoidance of the late complications of levodopa.
Motor fluctuations and end-of-dose dyskinesia can be reduced when dopamine agonists are used as add-on-therapy to levodopa. Significant improvements could be demonstrated according to the UPDRS-Score and the reduction of the daily “off-periods”.

Conclusions

The evidence of dopamine agonists for the treatment of Parkinson disease shows a good effecttiveness as monotherapy for new incidences and for additional use for older patients with more severe stages of the disease.
Levodopa use can be postponed for months until years. The dose of levodopa can be reduced for years and the reduced late complications of levodopa can be demonstrated.
Motor fluctuations and dyskinesia can be reduced statistically significant. Dopamine agonists can moderate movement disorders due to the disease.
Dopamine agonists are not recommended to be a substitute for levodopa. The effectiveness is too weak and too cost intensive. The use can be considered as cost-effective in the described fields of indication.