Movement Disorders
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DA Agonists - Ergot derivatives: Cabergoline

BASIC PHARMACOLOGY

MECHANISM OF ACTION

Cabergoline is an orally administered synthetic tetracyclic ergoline derivative that acts in vitro and in vivo as a selective D2 receptor agonist with no substantial affinity for D1 receptors. As with other ergotamine derivatives, it has also some affinity for non-dopamine receptors (noradrenergic and serotonergic).[1]

Cabergoline improves the symptoms of the primate model of Parkinson's disease (PD) after MPTP intoxication. Cabergoline lowers prolactin secretion, and like all effective D2-agonists, induces nausea, vomiting and orthostatic hypotension in healthy volunteers.[1]

PHARMACOKINETICS

One major characteristic of cabergoline is its long duration of effect with oral administration, probably because its elimination half-life is approximately 65 hours. For example, cabergoline is highly effective in suppressing prolactin levels with a duration of action up to 21 days after a single 1 mg oral dose. Such a pharmacokinetic profile allows a once-daily dosing treatment regimen. The cabergoline Tmax is observed at 2.5 hours, and it is metabolized into several metabolites excreted mainly by the fecal route.[1]

REVIEW OF CLINICAL STUDIES

PREVENTION OF DISEASE PROGRESSION

No qualified studies were identified.

SYMPTOMATIC CONTROL OF PARKINSONISM

MONOTHERAPY

To date, there are no Level-I, placebo-controlled studies that have investigated the efficacy of cabergoline as monotherapy. Two clinical reports were identified, but correspond to the same L-dopa-controlled study that performed two different analyses: one planned interim analysis at 1 year[2], and a final analysis at 3 to 5 years.[3] In this study, cabergoline was initiated as monotherapy, and L-dopa supplementation was added in patients if required (i.e. based on dose limiting adverse reactions and if they reached maximal dose of cabergoline).

Rinne et al. (1997)[2]: This is the only available study assessing the effects of cabergoline monotherapy (with secondary open L-dopa supplementation if needed) at one-year. It is a randomized, L-dopa-controlled (Level I), double-blind study conducted in 413 de novo patients with PD (mean age approximately 61 years). Cabergoline could be titrated up to 4 mg/d on a once a day regimen, and L-dopa up to 600 mg/d tid. Open label L-dopa supplementation was allowed during the course of the study. PD disability was evaluated using mean UPDRS (Unified Parkinson's Disease Rating Scale) scores and the CGI (Clinical Global Impression) scale. The proportion of patients experiencing a 30% decrease in parkinsonian disability and the proportion requiring the addition of L-dopa were also analysed. Thirty-seven (9%) patients withdrew from the study by 1 year. At this 1-year interim analysis, mean cabergoline daily dose was 2.8 mg/d and that of L-dopa was 468 mg/d. Thirty-eight percent of the patients received L-dopa supplementation in the cabergoline group (mean daily dose 305 mg/d). At baseline, UPDRS was 29.1 in the L-dopa and 27.5 in the cabergoline group. After 1-year of treatment, the decrease in scores was higher in the L-dopa (16.5) than in the cabergoline group (13.7). The difference between the two treatments groups was reported to be small (< 2.8 points) and there is no clear statistical comparison. Irrespective of L-dopa supplementation, 81% of the cabergoline patients and 88% of the L-dopa ones were clinically improved (30% reduction in UPDRS). CGI was rated similarly in both groups (61% of the patients being much improved with cabergoline and 67% with levodopa). The proportion of patients requiring L-dopa supplementation was greater in the cabergoline group (38%) than in the L-dopa group (18%, $p<0.01$). Both drugs had quite similar adverse event profiles, typical of dopaminergic side effects. Peripheral edema, gastric upset (nausea, vomiting, dyspepsia, gastritis) and dizziness were more frequent with cabergoline than L-dopa therapy. Sleep disorders, postural hypotension, confusion, and hallucinations were reported with the same frequency in both groups. This study had an overall quality rating score of 75%.

Rinne et al. (1998)[3]: In the long-term extension of the study reported above[2], over 400 subjects were followed for a minimum of 3 years. The primary end-point was the onset of motor complications, but antiparkinsonian efficacy was also monitored using the UPDRS Parts II and III. The withdrawal rate was 16% in cabergoline-treated patients and 13% in the L-dopa-treated patients. After 3 to 5 years of treatment (study endpoint), the mean daily dose of cabergoline was 3 mg/d and that of L-dopa 500 mg/d. 35 % of the patients still in the trial who were on cabergoline did not require L-dopa supplementation, compared with 52% in the L-dopa group. The authors reported that both treatments had comparable improved motor disability after 4 years, in the patients who completed the study; L-dopa recipients still showed on average 30% improvement in motor disability (UPDRS III), while treatment with cabergoline was associated with a 22% to 23% improvement versus baseline. However, no statistical analysis was provided. Adverse reactions were quite similar in both groups, with the most frequent reactions including nausea and vomiting, dizziness and hypotension, and sleep problems. Edema was more frequent in patients treated with cabergoline. This study had an overall quality rating score of 75%.

ADJUNCT THERAPY

Early Combination

No qualified studies were identified.

Late Combination

Two Level-I studies qualified for this analysis. One is a placebo-controlled trial and the other is a bromocriptine-controlled.

Hutton et al. (1996)[4]: This was the only large (188 patients with suboptimally controlled PD and end-of-dose deterioration or motor complications, mean age 63 years), 6-month, randomized, parallel group, placebo-controlled study identified in the search. The primary efficacy endpoint was change in UPDRS Part II and III, and changes in daily dose of L-dopa were also assessed. At the end of the study, cabergoline ADL (activities in daily living) scores were significantly better than those of placebo (12.3 [-19% from baseline] vs. 14.3 [-4% from baseline], p=0.032). The same difference in favor of cabergoline was also reported for UPDRS III (13.7 [-16% from baseline]) vs. 16.3 [-6% from baseline]; p=0.014). In the cabergoline group, the mean L-dopa dose was reduced by 175 mg/d as compared to placebo, where it was reduced by 25.5 mg/d. Adverse reactions were consistent with other drugs in the class and included those related to autonomic nerve system effects (more frequent with cabergoline than placebo), cardiovascular effects, and neuropsychiatric effects. This study had an overall quality score of 80%.

Inzelberg et al. (1996)[5] (This study was previously reviewed in the Bromocriptine section.): This was a 9-month, double-blind, parallel-group, randomized study performed in 44 patients showing increasing disability and motor fluctuations. Cabergoline (3.18 mg/d) and bromocriptine (22 mg/d) induced comparable improvement of most assessment criteria including ADL scores (cabergoline: from 11 at baseline to 9 at completion; bromocriptine: from 11 at baseline to 9 at completion, p<0.01 for both treatments), UPDRS III (cabergoline: from 35 at baseline to 28 at completion; bromocriptine: from 38 at baseline to 29 at completion, p<0.0001 for both treatments). None of these effects were significantly different between the 2 groups. The frequency of adverse reactions (typical of dopaminergic adverse reactions) was similar for both drugs. This study had an overall quality rating score of 52%.

PREVENTION OF MOTOR COMPLICATIONS

The only study identified that met the inclusion criteria was the final analysis (after 3 to 5 years of follow-up) of a larger randomized, L-dopa-controlled, Level-I study previously described (see Symptomatic Control of Parkinsonism). Below the data relevant to the effects of cabergoline in the prevention of motor complication are reviewed.

Rinne et al. (1998)[3]: 412 patients were randomized to treatment with cabergoline or L-dopa and followed for 3 to 5 years. The primary end-point was the onset of motor complications, which was confirmed at two subsequent clinic visits, and assessed on the basis of a complex and heterogeneous checklist in which fluctuations were classified into different categories (daily "wearing-off", nocturnal akinesia, early morning akinesia, "off" period freezing, peak-dose dyskinesia, early morning dystonia, dose-related "off" period dystonia, dose-related "on" dystonia, and random freezing, among others). At final analysis (3 to 5 year), the mean daily dose of cabergoline was 3 mg/d and L-dopa dose was 500 mg/d. Thirty-five percent of the patients that remained in the trial and who were treated with cabergoline did not require L-dopa supplementation as compared to 52% in the L-dopa group. Motor complications were statistically less frequent in the cabergoline arm (22 %) than in the L-dopa arm (34 %) (p<0.02). This study had an overall quality rating score of 75%.

CONTROL OF MOTOR COMPLICATIONS

The two Level-I studies already reviewed above in the section Control of Parkinsonism also qualified for review in this section. Therefore, only relevant data for control of motor complications will be reviewed here.

Hutton et al. (1996)[4]: This was 6-month, randomized, parallel, placebo-controlled study conducted in 188 patients with suboptimally controlled PD who had end-of-dose deterioration or other motor complications. Motor fluctuations were assessed as a secondary endpoint using item 39 of UPDRS Part IV (Complications of Therapy). Patients also kept diaries for "on" and "off" assessment. The cabergoline group at endpoint had significantly less "off" time compared with the placebo group (p=0.01), but no raw data were reported in the text. The amount of time spent "on", according to diaries, also increased significantly with cabergoline compared with the placebo group (p<0.05), but no actual data were reported in the text.

Inzelberg et al. (1996)[5]: This was a double-blind, parallel-group, randomized study performed in 44 patients showing increasing disability and motor fluctuations. "Off" periods were measured using diaries. Percentage "off" hours decreased with cabergoline (from 34% at baseline to 17% at completion) and bromocriptine (from 32% at baseline to 26% at completion, p<0.0001 for both treatments), and the differences between treatments was not statistically significant.

REVIEW OF SAFETY

Cabergoline has been associated with adverse reactions consistent with other dopaminergic agonists including gastrointestinal, cardiovascular and neuropsychiatric effects. There is no evidence that cabergoline has a safety profile different from other ergotamine derivatives like bromocriptine.

Similar to other dopamine agonists, it is likely that cabergoline aggravates dyskinesia in already dyskinetic, L-dopa-treated, patients although little data are reported in the literature that specifically address this issue. Conversely, when used as an initial therapy (before L-dopa) and regardless of subsequent L-dopa supplementation, there is some indication that cabergoline reduces the long-term risk of the occurrence of motor complications, especially dyskinesia.[3]

Few cases of fibrosis have been reported with cabergoline, as with other ergot compounds.[6,7]

Little data are available on "sleep attacks", and in selected clinical studies, sleep problems were reported without further details. One patient on cabergoline (and other antiparkinsonian and non-antiparkinsonian medications) was recently reported to have episodes that might correspond to "sleep-attack" episodes.[8]

In one study, edema was reported to be more frequent with cabergoline than with L-dopa.[3]

No data are available related to cabergoline and mortality.

CONCLUSIONS

Overall, less than 400 patients treated with cabergoline who were followed for a minimum of 6 months and up to 4 years were identified for inclusion in this review.

EFFICACY

PREVENTION OF DISEASE PROGRESSION

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of cabergoline regarding neuroprotection in patients with PD.

SYMPTOMATIC CONTROL OF PARKINSONISM

Monotherapy

No placebo-controlled studies have been done to assess the symptomatic efficacy of cabergoline as monotherapy in PD. There is only one identified L-dopa-controlled Level-I study.[2,3] In this study, patients received open-label levodopa supplementation to keep control of parkinsonian symptoms in both treatment arms, and therefore, there is INSUFFICIENT EVIDENCE to conclude on cabergoline efficacy for symptomatic control in PD.

Adjunct therapy in L-dopa-treated patients

Based on one large level-I placebo-controlled study[4] conducted in L-dopa-treated patients with motor fluctuations, cabergoline is considered as EFFICACIOUS in improving control of parkinsonian motor symptoms in advanced L-dopa-treated patients with PD. There is INSUFFICIENT EVIDENCE to conclude on cabergoline efficacy as an early combination therapy with levodopa in PD patients without motor fluctuations.

PREVENTION OF MOTOR COMPLICATIONS

Based on one 4-year L-dopa-controlled trial[3], initial treatment with cabergoline monotherapy with subsequent L-dopa supplementation is EFFICACIOUS in reducing the risk of occurrence of long-term L-dopa-induced motor complications.

CONTROL OF MOTOR COMPLICATIONS

Based on one Level-I, placebo-controlled trial[4] (which failed to include all the raw data on the "off" period), cabergoline is LIKELY EFFICACIOUS in controlling motor fluctuations in advanced L-dopa-treated patients with PD.

SAFETY

The clinical data available to date suggest that using and prescribing cabergoline in patients with PD carries an ACCEPTABLE RISK WITHOUT SPECIALIZED MONITORING. There is no indication that its safety profile differs from that of the other available dopamine agonists.

No data are available for use long-term (10 years) or on mortality.

IMPLICATIONS FOR CLINICAL PRACTICE

Cabergoline used initially as monotherapy in de novo patients with PD and later used with L-dopa supplementation is CLINICALLY USEFUL for reducing the risk of occurrence of long-term motor complications. The actual effect of cabergoline to control parkinsonism in early PD patients however remains INVESTIGATIONAL. After 3 to 5 years of treatment, only 20% of the patients can remain on cabergoline monotherapy and most patients need L-dopa.

As adjunct treatment in L-dopa-treated patients with motor fluctuations, cabergoline is CLINICALLY USEFUL in enhancing symptomatic control. The effect of cabergoline in controlling motor fluctuations is not fully documented.

In the studies reported herein, cabergoline was used at doses ranging from 2 to 5 mg/d. The clinical interest of cabergoline is the possibility to use it once daily, which is preferable for many patients; none of the other drugs in this class have a once-daily dosing regimen. Randomized, active comparator trials using other antiparkinsonian medications (e.g. dopamine agonists, MAO-B and COMT inhibitors) have not been done.

IMPLICATIONS FOR CLINICAL RESEARCH

In the literature there are few reports on the efficacy and safety of cabergoline. Additional studies are needed including:

- Well-designed, short-term, placebo-controlled study in L-dopa naïve PD patients to properly assess the magnitude of the effect of cabergoline on parkinsonian symptoms.
- Appropriate comparisons with other antiparkinsonian agents (other dopamine agonists, MAO-B and COMT-inhibitors).
- Studies comparing the risk of fluctuations and dyskinesias in patients treated with cabergoline versus treatment with other shorter-acting dopamine agonists (e.g. lisuride). The prolonged elimination half-life of cabergoline offers an advantage of once-daily dosing, but possible disadvantages with this treatment regimen are not well understood. For example, the prolonged elimination half-life might be a handicap in terms of wash-out of adverse events (like psychosis). These benefits vs. risks need to be further evaluated in prospective, controlled trials.
- Studies on the long-term quality of life impact of cabergoline, effects on mortality, and pharmacoeconomic benefits.

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