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[Intervention Review]

Lisuride for levodopa-induced complications in Parkinson's disease

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ABSTRACT

Background

Long-term levodopa therapy in Parkinson's disease is associated with the development of motor complications including abnormal involuntary movements and a shortening response to each dose (wearing off phenomenon). It is thought that dopamine agonists can reduce the duration of immobile off periods and the need for levodopa therapy whilst maintaining or improving motor impairments and only minimally increasing dopaminergic adverse events.

Objectives

To compare the efficacy and safety of adjuvant lisuride therapy versus placebo in patients with Parkinson's disease, already established on levodopa and suffering from motor complications.

Search methods

Electronic searches of MEDLINE, EMBASE and the Cochrane Controlled Trials Register. Handsearching of the neurology literature as part of the Cochrane Movement Disorders Group's strategy. Examination of the reference lists of identified studies and other reviews. Contact with Cambridge Laboratories and Roche Products Limited.

Selection criteria

Randomised controlled trials of lisuride versus placebo in patients with a clinical diagnosis of idiopathic Parkinson's disease and long-term complications of levodopa therapy.

Data collection and analysis

Data was to be abstracted independently by each author and differences settled by discussion.

Main results

No randomised controlled trials comparing lisuride with placebo in advanced Parkinson's disease with motor complications were found.

Authors' conclusions

Well designed randomised controlled trials demonstrating efficacy and safety are required before the use of lisuride in later Parkinson's disease can be supported.

BACKGROUND

Over 20 years after its introduction, levodopa remains the most effective therapy in Parkinson's disease. However, with long-term treatment, patients develop side effects comprised of motor and psychiatric complications. The former consist of involuntary writhing movements of the limbs and trunk (choreoathetosis), painful cramps often affecting the feet (dystonia) and a shortened response to each dose of levodopa (end-of-dose deterioration). These affect 50% of patients after 6 years of therapy (Rajput 1984) and 100% of young onset patients (Quinn 1986). In contrast, more recent work found motor complications in only 16% after 5 years of immediate or slow release levodopa therapy (Block 1997) suggesting we are now more cautious in our use of this agent.

An alternative treatment in Parkinson's disease is the dopamine agonist class of drug. These act directly on post-synaptic dopamine receptors in the striatum and so they do not require conversion into dopamine, as does levodopa. Unfortunately, they are less effective in clinical practice than expected, although they generate fewer motor complications when used as long-term monotherapy (e.g. Stern and Lees 1986; PDRG 1993). The use of dopamine agonists in newly diagnosed patients will be the subject of further Cochrane reviews.

Lisuride is an ergoline-based dopamine agonist like bromocriptine and pergolide. In a randomised controlled trial of 90 patients with early Parkinson's disease, over 4 years, lisuride monotherapy produced less dyskinesia and end-of-dose deterioration than levodopa, although it was less effective on parkinsonian disability (Rinne 1989). It was also hoped that, when added later in the course of the disease, lisuride would reduce off periods by virtue of a levodopa sparing effect and generate less motor complications than levodopa over the long-term.

A number of open label studies of lisuride as adjunct therapy to levodopa suggested it is capable of reducing off time. The present study has therefore been performed to provide a systematic review of all randomised controlled trials of adjunct lisuride therapy versus placebo in Parkinson's disease. A separate Cochrane review covers the effects of lisuride versus the active comparator bromocriptine.

OBJECTIVES

To compare the efficacy and safety of adjuvant lisuride therapy versus placebo in patients with Parkinson's disease, already established on levodopa and suffering from motor complications.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised trials comparing lisuride with placebo were considered for inclusion in the study.

Types of participants

Patients with a clinical diagnosis of idiopathic Parkinson's disease who had developed long-term motor complications of dyskinesia and/or end-of-dose deterioration. All ages were included. Any duration of levodopa therapy was included.

Types of interventions

Oral lisuride therapy or placebo. Trial durations of greater than 4 weeks were included.

Types of outcome measures

1. Improvement in the time patients spend in the immobile 'off' state.
2. Changes in dyskinesia rating scales and the prevalence of dyskinesia.
3. Changes in parkinsonian rating scales.

Many such rating scales exist. The Hoehn and Yahr scale (Hoehn and Yahr 1967) is usually used to classify the stage of the disease, but it is often used to follow the response to drug therapy. More recently, the Unified Parkinson's Disease Rating Scale (UPDRS 1987) has been used to score various disabilities and impairments due to the disease. Individual items from these scales were also used to provide more meaningful outcomes for patients reading this review.

4. Reduction in levodopa dose.
5. Number of withdrawals due to lack of efficacy and/or side-effects.

Search methods for identification of studies

1. The review was based on the search strategy of the Movement Disorders Group. This included computerised searches of MEDLINE and EMBASE and hand searching of appropriate neurology journals. Relevant trials were included on the Group's specialised register of randomised controlled trials. Further details are available in the Group's module on the Cochrane Database of Systematic Reviews.
2. The Cochrane Controlled Trials Register was also searched for relevant trials.
3. The reference lists of located trials and of other lisuride reviews were searched.
4. Additional assistance was provided by the drug manufacturer Cambridge Laboratories.

Data collection and analysis

The two authors (CC, JS) independently assessed the studies identified by the search strategy. Disagreements about inclusions were resolved by discussion. The full papers were to be assessed for methodological quality by recording the method of randomisation and blinding, whether an intention to treat analysis was used and the number of patients lost to follow up.

RESULTS

Description of studies

No randomised controlled trials comparing lisuride with placebo were found. Numerous open label, non-randomised and uncontrolled trials were located, but such studies are open to considerable bias and it was not felt appropriate to include them in this review.

Risk of bias in included studies

No randomised controlled trial was located comparing lisuride with placebo.

Effects of interventions

No randomised controlled trial was located comparing lisuride with placebo.

DISCUSSION

In the absence of any trials comparing lisuride with placebo in later Parkinson's disease with response fluctuations, it is impossible to assess whether lisuride is an effective treatment in this stage of the disease. The authors are unaware of any ongoing studies with lisuride in this area.

AUTHORS' CONCLUSIONS**Implications for practice**

No evidence from randomised controlled trials is available to demonstrate the efficacy and safety of lisuride in later Parkinson's disease.

Implications for research

Well designed randomised controlled trials demonstrating efficacy and safety are required before the use of lisuride in later Parkinson's disease can be supported.

ACKNOWLEDGEMENTS

The authors wish to thank the drug manufacturers Cambridge Laboratories and Roche Products Limited for their valuable assistance.

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WHAT'S NEW

Date	Event	Description
14 November 2008	Amended	Converted to new review format.

HISTORY

Review first published: Issue 2, 1999

Date	Event	Description
25 November 1998	New citation required and conclusions have changed	Substantive amendment

DECLARATIONS OF INTEREST

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Antiparkinson Agents [adverse effects] [*therapeutic use]; Dyskinesia, Drug-Induced [*drug therapy] [etiology]; Levodopa [adverse effects]; Lisuride [*therapeutic use]; Parkinson Disease [*drug therapy]

MeSH check words

Humans