

Short report

# Mesulergine and pergolide in previously untreated Parkinson's disease

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**SUMMARY** Seventeen hitherto untreated patients with mild Parkinson's disease were given the dopamine agonists mesulergine or pergolide. Of the 10 patients who received pergolide (mean dosage 3.7 mg/day) five failed to improve, four showed slight improvement and one gained moderate benefit. Of the seven patients who received mesulergine (mean dose 6.4 mg/day) three patients derived no benefit, two slight benefit and two moderate benefit. The incidence of adverse side-effects was high with both drugs despite the use of a peripheral dopamine receptor antagonist, domperidone, when required. These results are less encouraging than those reported from other centres both in respect of response rate and the severity of unwanted effects.

The role of dopamine receptor agonists in the treatment of Parkinson's disease, including their use in de novo patients remains controversial.<sup>1</sup> Much of the available literature concerns the use of bromocriptine.<sup>2-4</sup> Here we discuss our experience with two other dopamine receptor agonists, mesulergine and pergolide, in patients previously untreated with either levodopa or other agonist drugs. Mesulergine, a synthetic 8- $\alpha$ -amino-ergoline, stimulates D<sub>2</sub> receptors and is antagonistic to D<sub>1</sub> receptors. It appears to have a biphasic action with initial receptor antagonism followed, with increasing doses, by agonist effects.<sup>5</sup> The semi-synthetic ergot derivative, pergolide, is a long-acting and powerful dopamine agonist which unlike bromocriptine and mesulergine stimulates both D<sub>1</sub> and D<sub>2</sub> receptors.<sup>6,7</sup>

## Methods and results

### Mesulergine study

The seven patients (median age 69.5 years; males 2; females 5) had never taken levodopa, dopamine agonists or anticholinergic drugs. The mean duration of disease before treatment was 21.9 months, mean initial Hoehn and Yahr stages 2.3 (range 1-3) and mean Webster score 13.5 (9.5-16.0). The patients were

assessed at the beginning of treatment and then at subsequent visits, initially at fortnightly intervals and then after 3 months, every 6 weeks. Treatment was started with 0.1 mg of mesulergine bd and the dose increased slowly to maximum levels, reaching a mean maintenance dose of 6.4 mg of mesulergine. When required, domperidone was given before meals to combat nausea. The mean duration of treatment with mesulergine was 31.1 months (6-74 months). Routine haematological and biochemical investigations were carried out, a chest radiograph and electrocardiogram were checked at the beginning of treatment and at regular intervals thereafter. In the four patients who showed improvement, a single-blind placebo switch was carried out.

The results were assessed with respect to Webster scores and overall clinical impression and were divided into four categories: no response (no change in Webster score), slight benefit (10-25% reduction in Webster score), moderate benefit (25-50% reduction in Webster score) and excellent (50-100% reduction in Webster score). Three patients derived no benefit from mesulergine, two slight and two moderate benefit; one of the latter patients deteriorated markedly during placebo switch, the other three only slightly. When the medication was withdrawn by the manufacturers only two of the four patients still receiving the medication deteriorated significantly. Side-effects were common, sparing only two patients and consisted of nausea and vomiting despite antiemetics (three patients), lassitude (two patients), abdominal discomfort (one patient), depression (one

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patient), muzzy headedness (one patient), right bundle branch block (one patient), increased insulin requirement in diabetes (one patient). There were no other abnormalities detected from serial investigations.

#### *Pergolide study*

Ten patients (median age 65.5 years; male 3; female 7) who had received no previous anti-Parkinsonian treatment and who had a mean disease duration of 3.1 months were assessed in a similar manner to that employed in the mesulergine study. Their mean initial Hoehn and Yahr scale was 2.3 (range 1–3) and they had a mean Webster score of 12.6 (7.5–20.5). Treatment was started with 0.1 mg of pergolide twice daily after meals and increments were slowly made. The mean daily dose was 3.7 mg after a mean treatment period of 27.8 weeks (1 day–65 weeks). Patients were again divided into the same four categories. Five showed no benefit, four showed slight improvement, one gained moderate benefit; all five responders deteriorated to some degree on placebo switch. During the course of treatment, seven stopped pergolide because of intolerable side-effects, two within a few days of starting treatment. Two of the patients who were obliged to stop treatment had obtained some mild benefit, although the other five had failed to respond at the doses used. Adverse side-effects were common and included nausea and vomiting despite antiemetics (four patients), abdominal pain (two patients), nightmares (one patient), visual hallucinations (one patient), priapism (one patient), mild facial dyskinesia (one patient). The patient who had shown slight benefit on 0.5 mg of pergolide twice a day developed mild facial dyskinesias which curiously ceased when his pergolide was increased to 1 mg twice daily.

#### **Discussion**

Mesulergine has been studied in untreated Parkinsonian patients by several groups. Teravainen *et al*<sup>8</sup> described 11 patients in a placebo-controlled trial with slow standardised dose increments and an arbitrarily fixed maintenance dose of 7 mg daily. All improved with an average 30% reduction in disability scores confirmed by placebo switching. Tolerance to the drug was good overall and side-effects relatively insignificant, but including peculiar feelings in the head which were self-limiting in 42% of cases, insomnia in 25% and vasomotor disturbances in 17. Bonnet *et al*<sup>9</sup> studied 22 patients taking a mean daily dose of 8.1 mg. All improved with a mean 57% reduction in disability scores; nausea was the commonest side-effect (41%), which was promptly reversed by domperidone in all cases. Other side-effects in order

of frequency were feelings of imbalance (32%), flushing (27%), drowsiness (23%), headache (23%), and symptomatic postural hypotension (18%). The study of Rinne<sup>10</sup> included 11 patients all of whom improved to a degree. Tremor improved more than rigidity or bradykinesia and the drug was "relatively well tolerated". Schneider *et al*<sup>11</sup> included four untreated patients in their study using relatively large doses (mean 28.7 mg daily) of mesulergine and reported "moderate but definite benefit in all". Anorexia occurred in all the patients and nausea in three, but these symptoms improved spontaneously. In a recent double-blind study in 31 untreated patients mesulergine (mean dose 25 mg) was found to be two-thirds as potent as levodopa plus dopa decarboxylase inhibitor (mean dose 996 mg/day).<sup>12</sup> On-off effects and peak dose dyskinesias were not seen in the mesulergine-treated patients after follow-up periods up to 1 year. It is possible that these differences depend on the tolerance of individual investigators supervising the trial to the occurrence of side-effects and their decision in conjunction with that of the patient as to whether the drug should be stopped. Mesulergine has now been withdrawn by the pharmaceutical company because of the occurrence of testicular tumours in laboratory animals.

There are less published data on the results of pergolide treatment in de novo patients. Jeanty *et al*<sup>13</sup> included eight patients previously untreated with levodopa. Slow dosage increments were used and a mean of 2.9 mg daily was achieved. All patients "showed at least some improvement in rating scales", the mean improvement in Webster score being 21%; two patients experienced distressing psychiatric side-effects. Other side-effects included nausea, spontaneous erections, spontaneous ejaculations, insomnia and aggression, although it is not clear from the paper whether these side-effects affected only previously untreated patients as distinct from those who had taken other drugs. Quinn *et al*<sup>14</sup> described four untreated patients all of whom received domperidone, using a slow increment dosage regimen. Three patients improved with a 31% reduction in disability scores and one failed to improve on 10 mg of pergolide daily.

Our experience with these two dopamine receptor agonists has been disappointing, with a high incidence of side-effects despite the use of a slowly progressive drug regimen; particularly in the case of pergolide, the emergence of side-effects influenced the response rate, necessitating the withdrawal of medication at an early stage. It is of interest that despite treatment periods of over 2 years with mesulergine in four patients, no drug-induced dyskinesias or end-of-dose deterioration were observed.

The study with pergolide would suggest that it has

no appreciable advantages over bromocriptine in the management of mildly disabled de novo patients, supporting the view that D<sub>1</sub> receptors are unimportant in moderating the therapeutic response.

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