Extrapyramidal and depressive side reactions with flunarizine and cinarizine

Sir: In the past few years there have been several reports of extrapyramidal and depressive side reactions to cinarizine or its difluorinated derivate, flunarizine.\(^1\) We report a 30 month follow up study of patients receiving the drug. The symptomatic improvement in our 40 cases after stopping the drug support the belief that such side reactions were related to cinarizine or flunarizine.

We studied 40 patients, nine males and 31 females, with a mean age of 68.5 (SD 7) years. None had a history of extrapyramidal or depressive illness, when they were first given cinarizine or flunarizine. The "Symptoms and Signs Evaluation Scale"\(^2\) was used to rate the extrapyramidal defects giving scores to: tremor, rigidity, posture gait and autonomic signs. The worse the sign the higher is the score. The psychic depression was evaluated according to the Hamilton Scale\(^3\): absent (0), mild (+), moderate (+ +) and severe (+ ++). The orofacial dystonias were rated on the Fahn Marsden Scale.\(^6\)

The patients were arranged in five groups depending on their clinical state. In each one, we considered the mean time (in months) since the intake of the drug to the onset of the side reaction, the time needed for recovery after drug withdrawal and the percentage of patients on different doses of flunarizine and cinarizine. All data were analysed by the nonparametric method of Wilcoxon and Wilcoxon, describing for each one: the mean value (\(x\)), standard deviation (SD) and level of statistical significance (p).

**Group 1:** Twenty one patients had Parkinsonism of a mainly akinetic rigid type. The onset of the side effects was at 15-7 (SD 7) months and the time for recovery after drug withdrawal was 2-6 (SD 1-2) months.

**Group 2:** Eight patients had predominantly tremor with onset of side effects within 15 months of the beginning of the drug and recovery was about 2 (SD 0-5) months after drug withdrawal. The mean scores of each clinical feature in both groups had a p level of high significance (< 0.01) between the score at the onset and that reached at 30 and 60 days after drug withdrawal.

**Group 3:** In two cases the Parkinsonism deteriorated when they received flunarizine or cinarizine. This group was not considered for statistical analysis because of their previous pathological condition.

**Group 4:** Six patients suffered from orofacial tardive dyskinesia. In fig 1 we compare

\[ \text{Fig 1} \quad \text{Dyskinetic scores of each patient at onset and at 30 and 60 days after drug withdrawal. (according to Fahn Marsden Scale)}^9 \]

the score reached by each patient (number in brackets) according to the Fahn Marsden Scale at the onset and during the recovery period (30 and 60 days after drug withdrawal) showing a significant difference (p < 0.01) between them. (fig 1)

**Group 5** is a miscellaneous group of one rabbit syndrome, an akathisia and one acute dystonia that also recovered after discontinuation of flunarizine or cinarizine.

Thirty five patients suffered depression, six in a severe form, 17 moderate and 12 mild. There was no relationship between the severity of the extrapyramidal or depressive symptomatology and the amount of drug received or the total duration of treatment.

In fig 2, we compare an ascending curve of the percentage of patients developing extrapyramidal side effects since the beginning of the drug treatment and during a follow up period of 30 months (left) with a descending curve of the percentage of patients that recovered after drug withdrawal (right) (fig 2). In the curve of onset, two peaks are observed in the percentage of patients who had side effects at the 12th and the 24th months since beginning the drug. The number of patients who improved after withdrawal of the drug reaches its peak between 6 weeks and two months.

Thirty two patients (80%) developed extrapyramidal side effects with doses about 10 mg/day of flunarizine or 150 mg/day cinarizine and only eight patients exceeded those doses.

We conclude that: (1) The development of extrapyramidal signs are induced by flunarizine or cinarizine and that the improvement after drug withdrawal indicate a direct cause-effect relationship. (2) The onset of side effect was within 12 months in 70% of our cases. (3) Most of our patients (80%) received flunarizine or cinarizine in therapeutic dosage, so that overdosage could not be the cause of side effects.\(^{10\mbox{,}4}\) (4) The oromandibular tardive dystonias,
Therapeutic efficacy of a novel transdermal delivery system for (+)–PHNO in Parkinsonian squirrel monkeys

Sir: Serious difficulties in the management of progressive debilitation in advanced Parkinson's disease are caused by diminished benefit from levodopa ("wearing-off" effect) and sudden, unpredictable swings in neurological status ("on-off" effect). These conditions usually do not respond to conventional antiparkinsonian therapy, and indeed may develop as a consequence of nonphysiological, pulsatile stimulation by short-acting dopamine agonists.1 Recently, dramatic improvements in motor fluctuations have been reported following continuous intravenous or subcutaneous infusion of levodopa, lisuride, or apomorphine.1

Table: Plasma concentrations of (+)–PHNO (pg/ml) in a single squirrel monkey following application of transdermal patches covering a skin surface area of 2.4 or 9.6 cm².

<table>
<thead>
<tr>
<th>Skin surface area (cm²)</th>
<th>Time after patch application (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
</tr>
<tr>
<td>2.4</td>
<td>53</td>
</tr>
<tr>
<td>9.6</td>
<td>115</td>
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</tbody>
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References

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