Brocresine in Parkinson’s disease
Action of a peripheral and central decarboxylase inhibitor in potentiating levodopa

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SUMMARY  Brocresine, an aromatic L-amino acid decarboxylase inhibitor with both a peripheral and central action was shown to potentiate the therapeutic effect of levodopa in Parkinson’s disease. The search for useful decarboxylase inhibitors therefore need not be limited to agents that do not pass the blood/brain barrier.

The therapeutic action of levodopa in Parkinson’s disease is thought to depend on its ability to pass through the blood/brain barrier while dopamine cannot. Both peripherally and centrally, levodopa is converted to dopamine, assumed to be the active agent, by the action of aromatic L-amino acid decarboxylase. Inhibition of this enzyme by agents acting only peripherally would theoretically permit a higher proportion of absorbed levodopa to enter the nervous system and this effect has been verified in the experimental animal (Bartholini and Pletscher, 1968). A notable reduction in the required therapeutic dose of levodopa and abolition of the presumed peripheral side effects of catecholamines have been obtained using such an enzyme inhibitor (Gauthier, Ajuriaguerra, Simona, Constantinidis, Eisenting, Krassoevitch, Yanniotis, and Tissot, 1970; Siegfried, 1970) but these agents are not generally available. Conversely, central inhibition of decarboxylation of levodopa to dopamine should reduce or abolish the therapeutic effect.

Brocresine (4-bromo-3-hydroxybenzyl-oxyamino dihydrogen phosphate) has been investigated mainly for its action in inhibiting the formation of histamine from histidine but has a general action as an aromatic L-amino acid decarboxylase inhibitor (Lazare, 1972). This action is not confined to peripheral tissues, as in the experimental animal decarboxylase inhibition has been demonstrated in brain slices after administration of brocresine by several routes, detectable for many hours after a single dose and therefore unlikely to be due to contamination by blood, where activity declines rapidly (Wustrack and Levine, 1967; Ellenbogen, Stubbs, Markley, and Taylor, 1970). A central action has been demonstrated less directly by the inhibition of tremor induced by 5-hydroxytryptophan in mice, an effect not obtained by decarboxylase inhibitors that do not enter the brain (Hansson, Fleming, and Clark, 1965).

The object of this trial was to explore the possibility that an aromatic L-amino acid decarboxylase inhibitor with both peripheral and central actions might potentiate the therapeutic activity of levodopa. A full therapeutic trial could not be attempted.

METHOD

The trial was limited by restricted supplies of brocresine. It was not thought justified to treat patients already reasonably controlled on levodopa alone and six patients were chosen in whom there had been increasing difficulty in finding a dose of levodopa that would sufficiently control symptoms of Parkinsonism without intolerable dyskinesia. Thus all patients had initially been established on a higher dose of levodopa which subsequently had to be reduced to from 1 to 3-25 g a day, and all still had both Parkinsonism and distressing dyskinesia that was the limiting factor in dosage.

Brocresine was available in 100 and 25 mg tablets. In one patient levodopa was stopped for one week
and brocresine 300 mg thrice daily was then given alone for a further week. In the other patients the dose of levodopa was usually reduced and brocresine 300 mg daily added simultaneously. The dose of each drug was adjusted at frequent outpatient visits, or if necessary after admission to hospital for the initiation of the trial. The blood count, serum electrolytes and urea, and liver function tests were examined at intervals. Blood levels of levodopa were estimated by a method modified from that of Bertler, Carlsson, and Rosengren (1958) and Carlsson and Waldeck (1958). In five patients it was possible to compare levels at intervals after a dose of levodopa alone with those after an identical or smaller dose of levodopa combined with brocresine.

The patients had been attending regularly for systematic assessment of their disability by a battery of standardized tests, and their maximum level of function on levodopa alone was well known.

RESULTS

The only side-effect directly attributable to brocresine was epigastric burning in one patient on this drug alone. No disorder of blood count or blood chemistry was detected.

Brocresine 300 mg thrice daily without levodopa for one week had no therapeutic effect in the one patient in whom this was tried.

When brocresine and levodopa were given together, both the therapeutic effect and the incidence of dyskinesia could be altered by changing the dose of either drug, and it was not possible to use a standardized dosage of brocresine. The initial doses were, however, too high, leading to increasing overdosage with levodopa and eventually 50 to 300 mg a day in divided doses proved more satisfactory.

On the combined régime the dose of levodopa required to produce a comparable therapeutic effect was much reduced, ranging from one third to one fifth of the dose previously needed. Dyskinesia still proved to be the limiting factor in dosage. With improvement in symptoms of Parkinsonism equivalent to that achieved by the optimum dose of levodopa alone, dyskinesia was less troublesome in three patients, unchanged in one, and more readily provoked in two. The therapeutic advantage of combined therapy in these very difficult patients was therefore slight.

With the exception of intermittent hyperhidrosis in one patient, all symptoms usually attributed to the action of catecholamines outside the central nervous system—in particular, the nausea intermittently experienced by all these patients—were abolished.

On a single reading, no levodopa was detected in the blood of a patient who had taken brocresine 900 mg a day for one week. Blood levels of levodopa after varying doses of levodopa alone or combined with brocresine are shown in the Table. In patients 1 and 2, it was possible to compare the same dose with and without brocresine, and in these circumstances blood levels on the combined treatment were all higher by a factor varying from 2 to 80. When lower doses of levodopa were given with brocresine, blood levels were still generally higher than after higher doses of levodopa alone in the same patient, but when the dose of each substance was greatly reduced, as in patient 5, the point was reached where no increase in blood levels was obtained.

Correlation between blood levels of levodopa and clinical effect was difficult to establish, but

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose (mg)</th>
<th>Time after drug (hr)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>6</th>
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<td>0:15</td>
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<td>3:63</td>
<td>1:1</td>
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<td>1:7</td>
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<td>1:2</td>
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<td>5:5</td>
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</table>

when levels were consistently low, at 0.2 mg/ml. or less, there was no alleviation of the Parkinsonian state and no dyskinesia. When blood levels were consistently raised to 2.5 mg/ml. or higher, there was either notable clinical improvement without dyskinesia, or incapacitating dyskinesia, and often unpredictable fluctuations between these widely differing clinical states. At intermediate levels, no correlation with the clinical state could be detected.

**DISCUSSION**

The increased blood levels of levodopa and the abolition of nausea strongly suggest that brocresine inhibited aromatic L-amino acid decarboxylase in peripheral tissues in these patients. The reduction in the effective therapeutic dose of levodopa can be attributed to this peripheral effect, allowing more levodopa to enter the nervous system, and this suppression received some support from the clinical states observed to be associated with high and with low blood levels. No evidence of the central decarboxylase inhibitory action of brocresine observed in animal experiments could be obtained in this clinical trial, but if such central inhibition occurred in these patients, it did not interfere with the potentiation of the therapeutic effect of levodopa. The practical application of this finding is that the search for an aromatic L-amino acid decarboxylase inhibitor for therapeutic use need not be limited to substances that do not penetrate the blood/brain barrier.

The reduction or abolition of peripheral catecholamine effects when a peripheral decarboxylase inhibitor is given with levodopa is theoretically predictable, but Siegfried (1970) and Gauthier et al. (1970) have also observed a reduction in the dyskinesia that is justifiably assumed to be a central effect of levodopa. This reduction could not be consistently confirmed in the patients in the present small series, who were deliberately chosen as having escaped adequate control with levodopa alone. Such unexpected results, including the potentiating effect of a decarboxylase inhibitor capable of acting centrally, reported here, are not entirely compatible with the hypothesis of simple replacement therapy in Parkinson’s disease with centrally formed dopamine.

We are grateful to Smith and Nephew Limited for supplies of brocresine and for the estimation of blood levels of levodopa.

**REFERENCES**


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