operator gave an eight year history of attacks of unilateral headache with minimal nausea, lasting for up to two days. These occurred initially at intervals of two weeks, but then every three days. At first the attacks were preceded by a typical 25 minute visual aura, in which he experienced a coloured rotating diamond and zig zag lines, usually in the visual field. Since then, however, an increasing proportion of them have been preceded by a momentary feeling that his actual behaviour is unduly familiar, followed by a 20 minute sequence of unpleasant, almost morbid sensations that he felt he had come across before, as if in previous dreams, "in another world". This would be followed by some impairment of memory lasting for three days, and a rather milder, though sometimes more generalised headache with nausea that would last for one day. In addition some attacks were preceded by 15 seconds of quite intense giddiness and there have been a number of episodes of dysphasia. There have never been any lapses of concentration or impairment of consciousness, and he said he was able to carry on speaking and working while the aura was in progress. There is no focal deficit of migraine. He derived some benefit from pizotifen which seemed to shorten his aura, but was not helped much by methysergide.

There were no physical abnormalities on examination. A CT scan was normal and two EEGs showed a generalised excess of slow wave activity. Visual, sensory and motor symptoms, usually in that order of frequency, are the commonest seen in the aura phase of classical migraine. Occasional patients become dysphasic and some symptoms (for example, ataxia, dysarthria and vertigo) have been attributed to disturbances in the vertebro-basilar circulation. In one series of patients with transient global amnesia, 42% gave a past history of migraine, a figure considered significantly greater than the prevalence in the general population. It seems likely that some such cases, which are only rarely recurrent, are indeed manifestations of migraine while others are ischaemic in origin. Raskin describes a patient who experienced 15 episodes of transient global amnesia, each lasting up to six hours followed by headache, each after drinking a glass of red wine. While ophthalmic and auditory hallucinations have been described in the aura phase of classical migraine, recurrent transient memory disturbances of the type experienced by this patient, which are reminiscent of deja vu phenomena, do not appear to have been reported in detail, though Saut11 and Sacks12 allude to similar cases.

There is much, admittedly circumstantial, evidence that the cortical disturbances of classical visual field, due to spreading depression moving across the cortical surface, have speculated that transient global amnesia is due to a wave of spreading depression moving across the hippocampal surface. This patient's deja vu phenomena, which have a frequency and duration typical of classical migraine, are probably mediated similarly, and it is speculated that this is due to spreading depression in the temporal lobe. Migraine therefore should be considered among the causes of deja vu phenomena, particularly if prolonged.

Dr R Guilford made helpful comments on this manuscript.

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The second case was a 67 year old man who had had PD for 10 years. Eighty Madopar 62.5 mg tablets caused severe dyskinesias and untolerable headaches in the morning. Reducing the dosage to 6 tablets per day had nine hours off periods daily. Apomorphine was given initially by a "Penject" system and subsequently by subcutaneous infusion at a dose of 40 mg/day. Off periods for one hour daily and levodopa could be reduced from 400 mg daily to 300 mg daily. She has now been maintained on apomorphine infusion for 14 months with mild involuntary movements but no psychiatric side effects.

Case 3 was a 74 year old man with severe Parkinsonian tremor and bradykinesia who could not tolerate optimal doses of levodopa, bromocriptine or pimozide. Madopar in 120 mg three times daily caused nausea and psychosis, both during on and off phases. Bromocriptine 2.5 mg, three times daily caused visual hallucinations with confusional periods and the same patient, with benzhexol 2 mg, twice daily. He tolerated subcutaneous apomorphine infusion at 3 mg/hr for 12 hours daily and his tremor grading (modified King's College scoring system) improved from 3 to 0.5 (2.5 mg tablets/kg) along with improvement in his bradykinesia. Single blind infusion of normal saline in place of apomorphine resulted in a return of the severe Parkinsonism. His levodopa dosage could be reduced from 200 mg to 150 mg daily and he has been maintained on apomorphine for 14 months without any neuropsychiatric problems except for occasional nocturnal confusion.

Over the past two years we have treated 12 non-demented PD patients with refractory on-off oscillations, using subcutaneous apomorphine. Nine have continued treatment with apomorphine. Eight were resistant off treatment. The remaining four patients were maintained on oral apomorphine. Moderate levodopa dosage could be reduced from 300 mg to 60 mg daily and levodopa could be reduced from 400 mg daily to 300 mg daily. Eight patients have maintained levodopa dosage at 150 mg.
to be the treatment of choice in this subgroup of patients.

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4 Storai F, Micheler E, Beukert O. Tremor inhibition in parkinson syndrome after apomorphine administration under L-dopa and decarboxylase inhibitor basic therapy. Pharmacopsychiatr 1972;5:198-205.

Subcutaneous and sublingual levodopa methyl ester in Parkinson's disease

Subcutaneous continuous infusions or intermittent injections of the dopamine receptor agonist apomorphine have proved to be an effective treatment for motor fluctuations in patients with Parkinson's disease receiving long term levodopa treatment. Levodopa itself is impractical for chronic parenteral treatment because of its low solubility and high acidity. The highly soluble levodopa methyl ester (LDME), however, might be a more suitable candidate for parenteral application and its longer half-life compared with that of apomorphine could be of clinical advantage. We have therefore investigated the possibility of administering LDME subcutaneously and, following a previous anecdotal report, by the sublingual route.

Five sublingual and five subcutaneous doses of LDME were given to seven patients with idiopathic Parkinson's disease and motor fluctuations. Their mean age was 59 years, mean duration of disease 12 (4-22) years, mean duration of levodopa therapy 9.5 (1.5-19) years and mean stage of Hoehn and Yahr 3-4 when "off" and 2.4 when "on". All patients were known to respond to their first morning dose of 100 or 200 mg of oral levodopa plus decarboxylase inhibitor within 15 to 30 minutes and the mean duration of effect was 135 (90-120) minutes. On test days the morning dose was replaced by 1 ml of LDME (equivalent to 200 mg levodopa) either injected subcutaneously or given sublingually. Patients were given 50 mg of oral benserazide one hour before the LDME challenge. Subcutaneous doses were injected in two boluses of 0.5 ml each into different sites of the abdominal wall. With sublingual applications patients were instructed to keep the liquid underneath their tongue as long as possible and to swallow it as soon as they felt forced to swallow. Motor assessments were carried out using the modified Webster scale at baseline and at the time of maximum therapeutic effect as well as unilateral hand tapping tests 10 minutes before and every 10 minutes after administration of LDME until drug effects had completely worn off or up to one and a half hours when there was no clinical effect.

Two patients switched "on" with subcutaneous LDME with the same quality and duration of therapeutic effect seen after their oral levodopa doses. The time from injection to full switching was 60 minutes in both patients. Two patients had no effect over the entire observation period of 90 minutes and another one experienced onset-of-dose dyskinesias continuing for 110 minutes without ever switching fully "on." One of the responders then received a second injection which after a latency of 80 minutes produced some clinical effects with an inferior "on"-quality lasting for only 15 minutes. All patients had burning sensations at the injection site with rapidly developing nodules which slowly disappeared over two to four days.

Sublingual LDME was ineffective in all patients who managed to keep the liquid underneath their tongue for an average of 12 (5-20) minutes. No local side effects were observed.

The cause for the unpredictable response to subcutaneous LDME is unclear. The rate of de-esterification of LDME and resulting absorption of levodopa is influenced by pH, temperature and distribution and activity of esterases. Different individual conditions at the subcutaneous injection site may therefore be responsible for the varying clinical effects observed. As the local toxic reaction to subcutaneous LDME was seen in both responders and non-responders it is unlikely to be a major reason for poor absorption.

The failure of sublingual LDME to produce clinical effects provides no evidence for absorption through the oral mucosa.

Although the number of patients in this trial was small we conclude that due to the variability and unreliability of clinical response subcutaneous LDME is unlikely to become a practical treatment for fluctuating Parkinson's disease.

We gratefully acknowledge Chiesi Farmaceutica, Parma, Italy for providing levodopa methyl ester solution.

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Cortical nicotinic receptors in Alzheimer's disease and Parkinson's disease

Cognitive impairment and central cholinergic dysfunction are common features of Alzheimer's disease (AD) and Parkinson's disease (PD). Degeneration of subcortical-cortical cholinergic systems and reductions in cortical pre-synaptic cholinergic markers, such as choline acetyltransferase (CAT) activity, have been consistently demonstrated in AD and PD. Most investigations of muscarinic cholinergic receptors in the neocortex indicate that receptor binding is unchanged in AD and increased in PD. The status of nicotinic cholinergic receptors is less clear. We have examined nicotinic receptor binding and CAT activity in the cortex in AD and PD.

Brain tissue was obtained at necropsy from ten patients with AD and from ten matched control subjects with no evidence of neurological or psychiatric diseases, and from ten patients with PD, five of whom were clinically demented according to DSM III criteria, and ten matched controls. AD and PD were confirmed neuropathologically. The Parkinsonian patients had been treated with levodopa up to the time of death. Patients with AD and controls had not received any medication that is known to affect the central nervous system. Using washed and membrane homogenates we performed saturation analysis for nicotinic receptors with (3)H-nicotine (concentrations 0.5-64 nM) in the frontal cortex (Brodmann area 8) and temporal cortex (Brodmann area 38). Non-specific binding was defined by unlabelled nicotine. Protein concentrations and enzyme activities were measured by standard techniques.

CAT activity was reduced in the frontal and temporal cortex of patients with AD and demented and non-demented patients with PD (table). Cortical maximal densities of

<table>
<thead>
<tr>
<th>Control (n = 10)</th>
<th>AD (n = 10)</th>
<th>Control (n = 10)</th>
<th>PD (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>79 (8-24)</td>
<td>82 (7-23)</td>
<td>73 (1-5)</td>
</tr>
<tr>
<td>Death to brain removal (h)</td>
<td>40 (5-60)</td>
<td>42 (6-62)</td>
<td>19 (6-24)</td>
</tr>
<tr>
<td>CAT activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in frontal cortex</td>
<td>4 (0-07)</td>
<td>1 (0-08)*</td>
<td>4 (0-04)</td>
</tr>
<tr>
<td>in temporal cortex</td>
<td>4 (0-03)</td>
<td>1 (0-03)*</td>
<td>4 (0-02)</td>
</tr>
<tr>
<td>CAT activity (nicotine binding)</td>
<td>21 (7-13)</td>
<td>11 (0-14)*</td>
<td>23 (1-11)</td>
</tr>
</tbody>
</table>

Wilcoxon's rank-sum test: *p < 0.05.

CAT activity in nmoi/h/mg protein; nicotine binding as Bmax in fmol/mg protein.
Subcutaneous apomorphine for parkinsonian patients with psychiatric side effects on oral treatment.
K Ray-Chaudhuri, R J Abbott and P A Millac

*J Neurol Neurosurg Psychiatry* 1991 54: 372-373
doi: 10.1136/jnnp.54.4.372

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