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 more recently 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 right visual field, since then the duration and intensity of the aura has varied. At the moment of the aura he could not name objects, but his ability to move was intact.


dr R Guilfoff made helpful comments on this manuscirt.
to be the treatment of choice in this subgroup of patients.

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Subcutaneous and sublingual levodopa
methyl ester in Parkinson's disease

Subcutaneous continuous infusions or
intramuscular 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.2,3 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
application4 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
by the subcutaneous and, following a previous anecdotal report,4 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
dosing of 100 or 200 mg of oral levodopa or
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
dose. 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 swallow 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 respondents then received a second injection which after a latency of 80 minutes produced some
effectual clinical effects with an inferior "on"-quality lasting for only 15 minutes. All patients had
burning sensations at the injection sitewith
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 15
(5-20) minutes. No local side effects were
observed.

The cause for the unpredictable response
to subcutaneously administered LDME is not clear. A rate of de-esterification of LDME and resulting
absorption of levodopa is influenced by pH,
temperature and distribution and activity of
esterases. Different 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
respondents 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
dose-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 subcortico-
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.1 1 Most investigations of
muscarnic cholinergic receptors in the
neocortex indicate that receptor binding is
unchanged in AD and increased in PD.1 1
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
nervological 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-soluble plasma
homogenates we performed saturation
analysis for nicotinic receptors with (±)[3H]
icotine (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

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>Table Mean (SEM) maximal nicotinic receptor binding in the cortex</th>
<th>Control</th>
<th>AD</th>
<th>Control</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 10)</td>
<td>(n = 10)</td>
<td>(n = 10)</td>
<td>(n = 10)</td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>79 8 (2 4)</td>
<td>82 7 (2 3)</td>
<td>73 1 (5 5)</td>
<td>73 1 (2 5)</td>
</tr>
<tr>
<td>Dementia (score)</td>
<td>40 5 (6 0)</td>
<td>42 6 (6 2)</td>
<td>19 6 (2 4)</td>
<td>18 1 (2 7)</td>
</tr>
<tr>
<td>CAT activity</td>
<td>40 (0 7)</td>
<td>18 (0 4)*</td>
<td>4 2 (0 4)</td>
<td>2 3 (0 4)*</td>
</tr>
<tr>
<td>in frontal cortex</td>
<td>4 4 (0 3)</td>
<td>14 (0 3)*</td>
<td>4 5 (0 2)</td>
<td>2 5 (0 3)*</td>
</tr>
<tr>
<td>in temporal cortex</td>
<td>21 7 (1 3)</td>
<td>11 0 (1 4)*</td>
<td>23 1 (1 1)</td>
<td>12 2 (1 3)*</td>
</tr>
<tr>
<td>(-)[3H]nicotine binding</td>
<td>26 9 (1 1)</td>
<td>11 5 (1 2)*</td>
<td>25 0 (1 1)</td>
<td>13 3 (0 9)*</td>
</tr>
</tbody>
</table>

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

CAT activity in nmol/h/mg protein; nicotine binding as Bmax in fmol/mg protein.