

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 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.^{1,2} 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 application³ and its longer half-life compared with that of apomorphine could be of clinical advantage. We have therefore investigated the possibility of administering LDME both 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 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 spit it out 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 switch "on" 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 tongues for an average of 13 (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.⁵ 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.

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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.^{1,2} Most investigations of muscarinic cholinergic receptors in the neocortex indicate that receptor binding is unchanged in AD and increased in PD.^{3,4} 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 membrane homogenates we performed saturation analysis for nicotinic receptors with (-)-[³H]-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 Mean (SEM) maximal nicotinic receptor binding in the cortex

	Control (n = 10)	AD (n = 10)	Control (n = 10)	PD (n = 10)
Age (year)	79.8 (2.4)	82.7 (2.3)	73.1 (5.5)	73.7 (2.5)
Death to brain removal (h)	40.5 (6.0)	42.6 (6.2)	19.6 (2.4)	18.1 (2.7)
CAT activity				
in frontal cortex	4.0 (0.7)	1.8 (0.4)*	4.2 (0.4)	2.3 (0.4)*
in temporal cortex	4.4 (0.3)	1.4 (0.3)*	4.5 (0.2)	2.5 (0.3)*
(-)-[³ H]-nicotine binding				
in frontal cortex	21.7 (1.3)	11.0 (1.4)*	23.1 (1.1)	12.2 (1.3)*
in temporal cortex	26.9 (1.1)	11.5 (1.2)*	25.0 (1.1)	13.3 (0.9)*

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

CAT activity in nmol/h/mg protein; nicotine binding as B_{max} in fmol/mg protein.