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 application[3] 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)*
$(-)$-$[^3H]$-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 text: *p < 0·05.
CAT activity in nmol/h/mg protein; nicotine binding as B_{max} in fmol/mg protein.

nicotinic receptors [6] were substantially reduced in both AD and PD. There were no changes of the equilibrium dissociation constants (K_D).

The exact cellular location of nicotinic cholinergic receptors in the cerebral cortex is not known. The parallel changes in these receptors and CAT activity in AD and PD suggest that they are located pre-synaptically on degenerating cholinergic axons. This view is consistent with the finding that nicotine stimulates the release of acetylcholine from cholinergic terminals in the cortex.[5] The present results point to the potential for stimulation of the remaining nicotinic receptors as a treatment of the cholinergic deficit in AD and PD and provide a rationale for a therapeutic trial of selective nicotinic agonists.

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Industrial exposure to cobalt causing optic atrophy and nerve deafness: a case report

A 48 year old man presented with a seven month history of progressive bilateral deafness with tinnitus and occasional vertigo and a six month history of visual failure. He had been exposed to raw cobalt powder for 20 months, working 50 hours a week. He stopped work in November 1988. In spite of face masks, some of the powder was inhaled. He smoked ten cigarettes a day and drank two pints of lager a week. There was no drug exposure or family history of note. On examination his visual acuity was 6/36 in the right eye and 6/60 in the left eye. The temporal margins of the discs were pale. Hearing was impaired bilaterally. Full haematological investigation, chest radiograph and CT brain scan were normal. CSF showed a raised protein of 70 mgs/100 ml with oligoclonal IgG banding. Syphilis serology was negative. Blood cobalt was 234 µgm/l (normal <2) in February 1989, falling to 14·7 µgm/l by May 1989. Twenty four hour urinary cobalt was 119 µgm/24 hr (normal <51) in February 1989. VERs in February 1989 were right eye 125 ms, left eye 126·5 ms, in May 1989, 118 ms on both sides, and in February 1990, 109 ms on both sides. By January 1990 the visual acuity improved to 6/12 bilaterally.

Audiometry improved from December 1988 to February 1990 as shown. The patient felt his hearing was back to normal by the end of 1989.

Cobalt is a relatively rare metal. Today most of it is produced as a by-product of copper or silver production. Cobalt is widely used in the making of hard metals in industry, for example, drill tips and gas turbine blades. It is also used in medicine. The metal alloy, vitallium, is a strong and corrosion resistant metal used for prostheses in replacement bone surgery, for example, hip and knee joints.[1]

Cobalt has also been used clinically in the treatment of certain types of anaemia; when given to normal and anaemic patients it has produced a reticulocytosis. Medically, it has been used as an antidote for certain types of poisoning, such as cyanide, and as a potentiator of the action of antibiotics or hydrocortisone. Radium has virtually been replaced by Cobalt 60 for radiotherapy.[1]

Many adverse reactions have been reported following its clinical use, although there are remarkably few reports of severe poisoning as a result of industrial exposure. Reactions to cobalt have included anorexia, nausea and vomiting, diarrhoea, precordial pain, cardiomyopathy, skin rashes, flushing, nerve deafness, renal damage, hypothyroidism, asthma and pulmonary fibrosis and possible optic atrophy.[1-5] Despite the long list of adverse reactions, the complications that developed in this case, optic atrophy and nerve deafness, have never been reported to occur together.

Licht, Oliver and Rachmilewitz[4] described the only previous case report of optic atrophy possibly secondary to cobalt chloride. The patient, a 32 year old Jewish man, was found to have a pancytopenia with a hypercellular bone marrow of unknown aetiology. The anaemia responded to courses of cobalt chloride given on four different occasions. On two occasions the drug had to be discontinued because of nausea and vomiting. On the fourth occasion, after a fifteen week course of cobalt chloride, the patient began to complain of deteriorating vision. Ophthalmological findings and fluroscein angiography indicated the presence of optic atrophy and abnormal choroidal perfusion. Their patient had received a total dose of 73 g of cobalt chloride over a period of three years. Following cessation of the drug there was no further deterioration in vision despite the progression of the underlying disease, suggesting that the optic atrophy may have been due to cobalt toxicity.

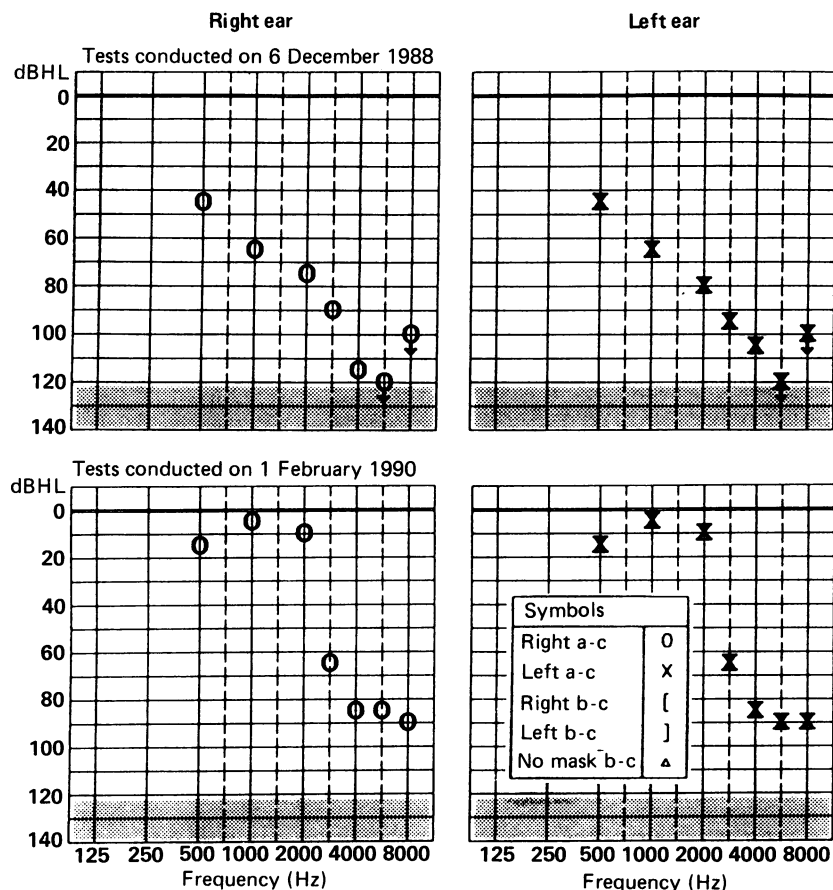Gardner[2] studied 17 patients with anaemia and uraemia treated with cobalt chloride.

Figure   Audiograms showing improvement of hearing after withdrawal from cobalt exposure.