thought of as harmless may therefore be toxic to a small proportion of the population who have an inability to metabolise them easily to safer compounds.

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- Casida JE, Gammon DW, Glickman AH, Lawrence LJ. Mechanisms of selective actions of pyrethroid insecticides. *Ann Rev Pharmacol Toxicol* 1983;23:413-38.
- Pall HS, Williams AC, Waring RH, Elias E. Motor Neurone Disease as manifestation of pesticide toxicity. *Lancet* 1987;ii:685.
- Hutson DH. The metabolic rate of synthetic pyrethroid insecticides in mammals. *Prog Drug Metab* 1979;3:215-52.
- Hathway DE. *Foreign compound metabolism in mammals*, vol 5. London: Chemical Society, 1979:156-8.
- Hutson DH, Casida JE. Taurine conjugation in metabolism of 3-phenoxybenzoic acid and the pyrethroid insecticide cypermethrin in mouse. *Xenobiotica* 1978;8:565-71.
- Steventon G, Waring RH, Williams AC, Pall HS, Adams D. Xenobiotic metabolism in motorneurone disease. *Lancet* 1988;ii:644-7.

(+)-PHNO: a new anti-Parkinsonian agent which does not induce chorea in MPTP-treated squirrel monkeys

Exciting advances in drug delivery technology to control fluctuations in response to anti-Parkinsonian therapy are under way.¹ One recent development is a rate-controlled transdermal delivery system for the selective

D₂ agonist (+)-PHNO which was capable of maintaining stable plasma levels in the therapeutic range throughout a 24 hour period in primates.² The suitability of (+)-PHNO for rate-controlled absorption through the skin sets it apart from conventional anti-Parkinsonian agents. However, as well as "on-off" swings, many Parkinsonian patients also have debilitating drug-induced dyskinesias, especially chorea.³ The pathophysiology of this side-effect is poorly understood. We now report that (+)-PHNO, unlike levodopa, does not induce chorea in MPTP-treated squirrel monkeys.

The subjects had previously served in experiments using transdermal application of (+)-PHNO² and had all received intermittent exposure to levodopa during the two years before this study (total exposure ranged from 70 to around 1500 mg/kg po for different animals). Locomotor activity and drug-induced choreoathetosis in each limb was scored continuously by direct observation every five minutes for up to three hours using a clinically-based rating scale of 0-4 according to frequency and severity. Dyskinesias in each limb were rated separately as follows: 0 = absent; 1 = occasional/mild; 2 = intermittent/moderate; 3 = frequent/marked; 4 = continuous/severe. Levodopa was administered by oral gavage at 5, 10, 15 or 20 mg/kg 1h following treatment with double the respective dose of carbidopa. (+)-PHNO was examined at 0.625, 1.25, 2.5 or 5 µg/kg sc in the leg.

Administration of levodopa caused a dose-dependent increase in locomotor activity accompanied by choreoathetoid movements affecting the limbs, especially the legs. These reached a peak some 40-60 minutes after treatment and were characterised by repetitive flexion/extension or circling movements of the hands, forearms, hindlegs and feet and gyration about the pelvis. Buccolingual dyskinesias were not observed. Chorea appeared less severe at the highest dose of levodopa (20 mg/kg) due to the emergence of verticalisation or climbing behaviour between 90 and 165 minutes after treatment. In contrast, treatment with (+)-PHNO induced marked locomotor stimulation, but no chorea was observed in the limbs at any dose examined (see table). Unlike levodopa, lashing movements of the tail were observed following treatment with (+)-PHNO; the relevance of these movements for dyskinesias in humans is not clear.

The absence of chorea in MPTP-treated squirrel monkeys following acute administration of the D₂-selective agonist (+)-PHNO agrees with a similar finding using chronic treatment with bromocriptine for five months in macaques.⁴ Similarly, in stage I-III Parkinsonian patients, Stoessl *et al*⁵ did not make any mention of dyskinesias following acute single dose oral treatment with (+)-PHNO. Interestingly, the less selective D₂ agonist apomorphine has been reported to reduce

chorea in Parkinsonian patients receiving levodopa therapy,⁶ in Huntington's disease⁷ and in neuroleptic-induced tardive dyskinesia.⁸ However, it should be noted that dyskinesias have occasionally been observed after administration of (+)-PHNO both in primates⁹ and in humans.¹⁰ The reason for this discrepancy is not known, but may be related to the severity of Parkinsonism, duration of prior treatment with levodopa ("priming"), and type of dyskinesia (chorea or dystonia).

Our findings, and those of others, clearly indicate a difference between the effects of a nonselective, indirect agonist (levodopa) and D₂-selective direct agonists in the genesis of chorea in the Parkinsonian brain. One interpretation of these findings is that stimulation of D₁ receptors may induce chorea. D₁ binding sites are particularly high in the medial pallidal segment,¹¹ an area implicated in the induction of chorea.¹² It is also of interest that the direct nigropallidal dopamine pathway is relatively unaffected by the neurotoxin MPTP,¹³ and this could provide a direct route for the production of chorea by levodopa.

We would predict that use of a directly acting selective D₂ agonist such as (+)-PHNO via a sustained release preparation in de novo Parkinsonian patients might greatly reduce the incidence of both chorea and motor fluctuations whilst giving effective relief from akinesia.

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- Stahl SM, Wets KM. Recent advances in drug delivery technology for neurology. *Clin Neuropharmacol* 1988;11:1-17.
- Rupniak NMJ, Tye SJ, Jennings CA, *et al*. Therapeutic efficacy of a novel transdermal delivery system for (+)-PHNO in Parkinsonian squirrel monkeys. *J Neurol Neurosurg Psychiatry* 1989;52:289-90.
- Markham CH. The choreoathetoid movement disorder induced by levodopa. *Clin Pharmacol Therap* 1971;12:340-3.
- Bedard PJ, Di Paolo T, Falardeau P, Boucher R. Chronic treatment with L-DOPA, but not bromocriptine induces dyskinesia in MPTP-Parkinsonian monkeys. Correlation with ³H-spiroperone binding. *Brain Res* 1986;379:294-9.
- Stoessl AJ, Mak E, Calne DB. (+)-4-propyl-9-hydroxynaphthoxazine (PHNO), a new dopaminomimetic, in treatment of Parkinsonism. *Lancet* 1985;ii:1330-1.
- Duby SE, Cotzias GC, Papavasiliou PS, Lawrence WH. Injected apomorphine and orally administered levodopa in Parkinsonism. *Arch Neurol* 1972;27:474-80.
- Corsini GU, Onali PL, Masala C, Cianchetti C, Mangoni A, Gessa GL. Apomorphine hydrochloride-induced improvement in Huntington's chorea. *Arch Neurol* 1978;35:27-30.

Table Induction of locomotor activity and chorea following treatment with levodopa or (+)-PHNO in MPTP-treated squirrel monkeys

	Levodopa (mg/kg po)					(+)-PHNO (µg/kg sc)				
	Vehicle	5	10	15	20	Vehicle	0.625	1.25	2.5	5.0
	Score summed over 180 minutes					Score summed over 75 minutes				
Locomotor activity	9 (10)	21 (6)*	34 (6)*	45 (8)*	31 (5)*	14 (4)	24 (6)*	28 (3)*	35 (3)*	42 (2)*
Chorea	0	4 (2)	64 (20)*	188 (24)*	156 (28)*	0	0	0	1 (1)	0

Values are expressed as the mean (1 SEM) for data obtained using seven animals.

*p < 0.01 compared to vehicle treatment, Dunnett's multiple comparison test.

- 8 Gessa R, Tagliamonte A, Gessa GL. Blockade by apomorphine of haloperidol-induced dyskinesia in schizophrenic patients. *Lancet* 1972;ii:981-2.
- 9 Clarke CE, Boyce S, Robertson RG, Sambrook MA, Stahl SM, Crossman AR. Behavioural effects of (+)-4-propyl-9-hydroxynaphthoxazine (PHNO) in primates rendered parkinsonian with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). *Arch Pharmacol* 1988;338:35-8.
- 10 Grandas Perez FG, Jenner PG, Nomoto M, et al. (+)-4-propyl-9-hydroxynaphthoxazine in Parkinson's disease. *Lancet* 1986;i:906.
- 11 Graham WC, Crossman AR. Autoradiographic localisation of dopamine D₁ binding sites in areas receiving striatal input. *Eur J Pharmacol* 1987;142:479-81.
- 12 Robertson RG, Farmery SM, Sambrook MA, Crossman AR. Dyskinesia in the primate following injection of an excitatory amino acid antagonist into the medial segment of the globus pallidus. *Brain Res* 1989;476:317-22.
- 13 Parent A, Lavoie B, Smith Y, Bedard P. The dopaminergic nigropallidal projection in primates: distinct cellular origin and relative sparing in MPTP-treated monkeys. In: Streifler, ed. *Adv Neurol*, Vol XX. New York: Raven, 1989.

Delayed-onset posthemiplegic dystonia and imitation synkinesia

The late development of hemidystonia following hemiplegia is an uncommon sequela of stroke.¹ Its pathogenesis is still controversial but may involve lesions in the contralateral caudate nucleus, lentiform nucleus, and thalamus, or combinations of these.² Imitation synkinesia was defined by Marie and Foix as "involuntary symmetrical movements tending to reproduce on one side of the body, movements executed by the other."³ It is usually associated with a thalamic or parietal lesion.⁴ We report a patient who developed a previously undescribed association of hemidystonia and imitation synkinesia as a late complication of a thalamic haemorrhage.

A 74 year old man with a three year history of hypertension developed acute headache, right hemiplegia, and hemianaesthesia in October 1982. The right limbs were hyperreflexic and the right plantar response extensor. Computed tomography (CT) showed a left thalamic haematoma with involvement of the internal capsule. Two months later, the patient was able to walk with crutches although his hemianaesthesia remained unchanged. Six months after the stroke, he developed voluntary pulling and twisting movements in his right arm and shoulder. Progressively, the involuntary movements spread to the neck, mouth, tongue, and the right side of his face. As a result, he had slight difficulty with speech and in swallowing. His eyelids intermittently screwed up forcefully, especially on the right side. His right leg was deformed, with a flexed knee, extended ankle, and clawed foot. Because of the leg dystonia, he found it difficult to walk and was almost confined to a wheel-chair from November 1984. Burning paraesthesia gradually developed in his arm and leg and his body. In August 1985, the patient's dystonic right hand started to imitate involuntarily simple movements that were performed by the left hand, such as waving fingers.

In December 1986, he was admitted because of increasing swallowing disturbance, hemidystonia, and paraesthesia of the right arm and leg. On examination, he was

Figure Surface EMG recordings. a) simultaneous contraction of right (imitative contraction) and left abductor pollicis brevis (APB); b) simultaneous contractions of right wrist extensor (WE, imitative contraction) and left anterior tibialis (AT). Arrows; indicating the flash signal to start voluntary contractions.

alert and intellect was not impaired. His cranial nerves were intact and eye movements were full and the optic fundi were normal. Mild hemiparesis and hyperreflexia without muscle atrophy were noted in the right limbs but plantar responses were flexor. All sensory modalities were diminished in the right side of the body and in the right extremities. His right shoulder was adducted and fixed, and the elbow was slightly flexed. The forearm was deformed with a flexed wrist and hyperextended fingers, particularly seen in an outstretched position. There were orolingual dystonia, bilateral blepharospasm, and grimacing of the right side of his face. Waving his left hand voluntarily, the patient simultaneously waved his right hand unintentionally. These imitative movements of the right hand could also be induced by moving either foot but not by passive movement of the left hand or either foot.

Routine haematological, electrolyte, and liver and renal function tests were normal. Serology for syphilis was negative. A chest radiograph was normal. CT showed hypodensity in the left thalamus. Surface EMG recordings showed simultaneous muscle activities on both right and left abductor pollicis brevis, when the patient was asked to abduct his left thumb (fig 1a). Similarly, there were muscle activities on the right wrist extensor muscles simultaneous with left anterior tibialis during dorsiflexion of the left foot (fig 1b). An EEG showed diffuse slow waves. Somatosensory evoked potentials (SEP) following stimulation of the left median and tibial nerves were normal. No

cortical SEP was obtained following the right median or tibial nerve stimulation. Daily regimens of 6 mg diazepam, 300 mg levodopa, 6 mg haloperidol, 15 mg baclofen, 75 mg dantrolene, 300 mg phenytoin and 600 mg carbamazepine had been tried without effect.

A left stereotaxic thalamotomy was performed in January 1987. Post-operatively, there was marked improvement in the orofacial dystonia, blepharospasm, hemidystonia, imitation synkinesia and in the burning paraesthesia in the right limbs. The mild hemiparesis and hemidystonia, and hemianaesthesia persisted. Two weeks after operation the patient was able to take food without difficulty and to walk with support. He remained in the same condition, without medication, two years after the operation.

The points of particular interest in this patient were first, the unique association of the late development hemidystonia with imitation synkinesia in the hemiparetic limbs and, second, the marked improvement of both involuntary movements after stereotaxic thalamotomy. These two observations may indicate that hemidystonia and imitation synkinesia share a common pathogenesis.

Disorganisation of the lemniscal system at any level may be responsible for imitation synkinesia.⁴ This might be a plausible explanation for the appearance of imitation synkinesia on the right hand with ipsilateral hemianaesthesia in our patient with thalamic haemorrhage. However, it is difficult to explain the distinct improvement of imitation synkinesia after stereotaxic thalamotomy.

Burke *et al* has suggested that delayed onset dystonia is the result of slowly evolving aberrant neuronal sprouting, stimulated by the original lesion.⁵ In our patient, the effect of thalamotomy may have been the result of removal of such aberrant neuronal sprouting, leading to the relief of hemidystonia.

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- 1 Dooling EC, Adams RD. The pathological anatomy of posthemiplegic athetosis. *Brain* 1975;98:29-48.
- 2 Marsden CD, Obeso JA, Zarranz JJ, Lang AE. The anatomical basis of symptomatic hemidystonia. *Brain* 1985;108:463-83.
- 3 Marie P, Foix C. Les syncineses des hemiplegiques. *Rev Neurol* 1916;1:13-27.
- 4 Cambier J, Dehen H. Imitation synkinesia and sensory control of movement. *Neurology (Minneapolis)* 1977;27:646-9.
- 5 Burke RE, Fahn S, Gold AD. Delayed-onset dystonia in patients with "static" encephalopathy. *J Neurol Neurosurg Psychiatry* 1980;43:789-97.

Magnetic resonance imaging in adrenoleukodystrophy presenting as spinocerebellar degeneration

Magnetic resonance imaging of a patient with adrenoleukodystrophy, presenting as spinocerebellar degeneration, showed symmetrical lesions in the corticospinal tract and cerebellar white matter adjacent to the dentate nuclei. These findings differentiate