

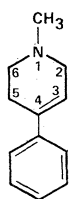
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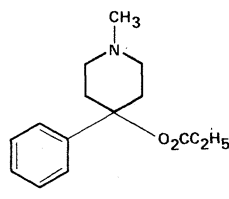
Chronic Parkinsonism in Humans Due to a Product of Meperidine-Analog Synthesis

Abstract. *Four persons developed marked parkinsonism after using an illicit drug intravenously. Analysis of the substance injected by two of these patients revealed primarily 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) with trace amounts of 1-methyl-4-phenyl-4-propionoxy-piperidine (MPPP). On the basis of the striking parkinsonian features observed in our patients, and additional pathological data from one previously reported case, it is proposed that this chemical selectively damages cells in the substantia nigra.*

1-Methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) is a commercially available compound that is sold as a chemical intermediate (1). The biological effects of this substance seem not to have been systematically investigated in animals or in man. MPTP is also a by-product in the synthesis of 1-methyl-4-phenyl-4-propionoxy-piperidine (MPPP), a meperidine analog (2). Admixed with varying amounts of MPPP, MPTP was recently sold as a new "synthetic heroin" in a limited region of northern California and used intravenously by a number of addicted individuals who subsequently developed severe parkinsonism. In this report we describe four of these patients, each of whom has been examined and followed by one or more of us.



MPTP



MPPP

The patient group consisted of one female and three males, whose ages ranged from 26 to 42 years. Each patient had a history of previous heroin abuse (3 months to 14 years). Patients 1 and 2 obtained a "new heroin" sample in San Jose, California, on 1 July 1982; patients 3 and 4 (brothers) received theirs in Watsonville, California, about 3 weeks earlier. Dosages ranged from 5 g over 4 days (cases 1 and 2) to 20 g over 5 to 8 days (cases 3 and 4). All patients became symptomatic within a week after starting

to use the new drug. First symptoms included almost immediate visual hallucinations (one patient), jerking of limbs (two patients), and stiffness (one patient). Generalized slowing and difficulty in moving occurred within 4 to 14 days after the initial use of the substance. In at least one patient, symptoms continued to evolve over a period of 3 to 5 days after the drug was stopped.

Three of the four patients were hospitalized within 14 days to 6 weeks of first use of the drug. Examination in each revealed near total immobility, marked generalized increase in tone, a complete inability to speak intelligibly, a fixed stare, marked diminution of blinking, facial seborrhea, constant drooling, a positive glabellar tap test, and cogwheel rigidity in the upper extremities. One patient exhibited a "pill-rolling" tremor (5 to 6 cycles per second) at rest in the right hand. All patients exhibited a flexed posture typical of fully developed Parkinson's disease. The fourth patient (case 4) was seen as an outpatient 4 weeks after onset of symptoms. He was able to walk but exhibited a short-stepped, slow, shuffling gait, "en bloc" turning, and generalized bradykinesia. In our examination of him, he was otherwise similar to the other three patients.

Additional findings in these patients included apraxia of eyelid opening in three patients (3) and limitation of vertical gaze in two patients. Electroencephalograms were normal in three patients; a fourth exhibited intermittent bitemporal slowing. Results of cerebral computerized tomography were normal in the

three patients who underwent the procedure. Lumbar puncture revealed an elevated protein in three of the four patients (range 47 to 120 mg/dl). Tests for Wilson's disease were negative in all four patients. Complete toxic screens for acidic, neutral, and basic drugs in plasma and urine including phenothiazines were negative in the two patients tested (4). Heavy metal screens in these two patients were also negative.

All patients responded to therapy with a combination of L-dopa and carbidopa (Sinemet). Addition of dopamine agonist therapy (bromocriptine or lisuride) provided additional therapeutic response in two patients. Five months after onset, none of these patients have shown signs of remission. All continue to require substantial doses of these medications, and one patient is now experiencing dose-limiting side effects. One patient (case 3) had all medications stopped 2 months after onset of symptoms for 5 days. During this period the patient completely reverted to his original state of complete immobility and rigidity, being able to move only his eyes. Swallowing was impaired to the point that he required intravenous hydration until his medications could be effectively resumed.

Analyses of all drug samples were performed by using thin-layer chromatography (TLC), gas chromatography (GC), and combined gas chromatography and mass spectrometry (GC/MS). Both MPTP and MPPP were identified by means of GC/MS (Fig. 1). Confirmation and quantitation was performed with reference material obtained from Aldrich Chemical Company (1) and the National Institute of Mental Health (5). A sample of the powder which was injected by patients 1 and 2 was obtained from their residences. This white crystalline powder contained 3.2 percent MPTP and 0.3 percent MPPP (by weight).

Three additional samples were obtained from the individual who supplied drugs to patients 3 and 4. These samples were said to contain the same substance our patients had been taking when symptoms developed and additional amounts of "good heroin" (presumably the target compound, MPPP) which had been added later to make it more salable. These brown granular samples also contained MPTP at concentrations ranging between 2.5 and 2.9 percent (by weight). They also contained large amounts of MPPP (between 22 and 27 percent by weight). No other drugs were detected in any of the samples analyzed.

A case reported by Davis *et al.* (6) has great bearing on the patient material re-

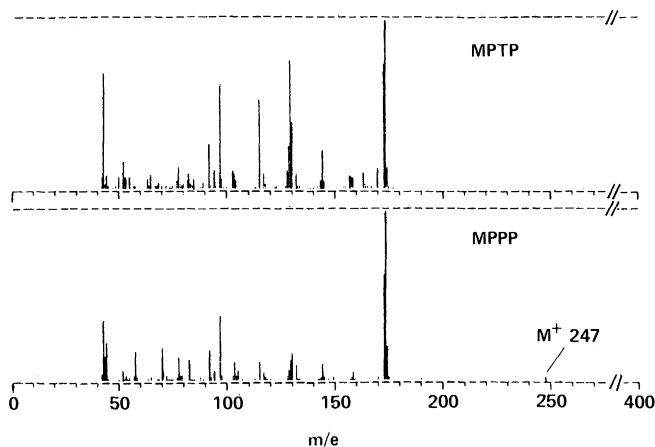


Fig. 1. Mass spectra of MPTP and MPPP.

ported here. Their patient was a graduate student who produced his own drugs. For 4 to 6 months he had been synthesizing MPPP (using a reaction which produced MPTP as a by-product) and injecting it intravenously without problems. Apparently, after taking several "shortcuts" in synthesis and injecting the resulting product, he developed marked parkinsonism. After repeating the student's synthetic methods, it was concluded that he had injected a mixture of 1-methyl-4-phenyl-4-hydropiperidine, MPPP, and MPTP (6).

The powders used by our patients were believed to be the products of a clandestine laboratory attempting to produce MPPP by the previously cited synthetic method (2). In this synthesis the percentage of MPTP formed is dependent on reaction conditions (2, 6). More vigorous conditions result in a higher percentage of MPTP formed. Analysis of a sample taken from this illicit laboratory shortly after these cases were identified revealed virtually pure MPTP (7).

We suspect that MPTP is the offending agent in these patients for several reasons. First, MPTP was the major component in the material injected by patients 1 and 2. Second, MPTP was also present in almost identical concentrations in the material which patients 3 and 4 were said to have taken. Third, MPTP was likely to have been present in the substance injected by the previously reported student when he became symptomatic (6). Finally, it was known to be available locally in relatively pure form.

It seems less likely that MPPP is the offending agent since it was present in only trace amounts in the powder taken by two of our patients. Further, MPPP was probably added to the substance taken by patients 3 and 4 at a later time. Intravenous use of MPPP by the previously reported graduate student for a period of 5 to 6 months did not result in

this syndrome (6). Last, MPPP bears a great similarity to the analgesic alphaprodine (Nisentil), differing only by the absence of a methyl group in the position 3. Although alphaprodine is used as an intravenous analgesic, we have been unable to find any reports of similar effects from the drug. However, for determination of the exact neurotoxicity of these substances, animal studies will be required.

Crucial to understanding of the biological effects of this compound are the neuropathological findings in the case reported by Davis *et al.* (6). Their patient died of a drug overdose 2 years after the onset of his parkinsonism. Destruction within the substantia nigra with neuromelanin pigment within microglial cells and a structure resembling a Lewy body were reported. We have reviewed this material (with Lysia S. Forno, M.D.) and confirmed the nerve cell degeneration in the substantia nigra. Moderately severe nerve cell loss was comparable in severity to that usually seen in idiopathic parkinsonism. There was abundant extraneuronal melanin pigment and a considerable astrocytic response with focal glial scarring. The changes were present throughout the compact zone of the substantia nigra but were more severe in the caudal portion. A single eosinophilic body, perhaps representing a Lewy body, was found. In contrast to cases of idiopathic parkinsonism the locus coeruleus and dorsal motor vagus nucleus were essentially normal.

It appears likely that similar cell damage has occurred in our patients. We base this opinion on the clinical similarity between our cases and the pathologically studied patient, and the fact that all of our patients continue to be symptomatic at five or more months after the initial insult. All continue to require the previously mentioned medications. The elevated spinal fluid protein seen in three

of our patients [as well as the case reported by Davis *et al.* (6)] is also suggestive of neuronal damage (rather than being a simple receptor blockade such as occurs with phenothiazines). The response to dopamine precursors and agonists in our patients would suggest that the striatum is at least partially spared, a situation analogous to Parkinson's disease.

Documenting the potential neurotoxicity of MPTP and possibly MPPP is important for several reasons. First, it should aid in the identification of the substance and management of future such cases should they occur. There may be additional attempts to manufacture meperidine analogs, and this substance may again appear in the illicit drug market. Second, this drug appears to be remarkably selective in its neurotoxic effects. Given the pathologically studied case, the relative purity of the clinical syndrome seen in our patients, and its remarkable clinical resemblance to Parkinson's disease, the drug may be of value in producing an animal model of Parkinson's disease. Finally, understanding of its mechanism of action might shed some light on the etiology of Parkinson's disease. An endogenous substance accumulating in the brain might have properties similar to these substances, thereby causing selective cell death in the substantia nigra with resulting parkinsonism.

J. WILLIAM LANGSTON
PHILIP BALLARD

Department of Neurology,
Stanford University School of
Medicine, Stanford, California 94305,
and Santa Clara Valley Medical
Center, San Jose, California 95128

JAMES W. TETRUD

612 Frederick Street,
Santa Cruz, California 95062

IAN IRWIN

Drug Assay Laboratory,
Stanford University Hospital,
Stanford, California 94305

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