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L-DOPA Poisioning

The medical therapy for Parkinson's disease, especially in younger patients, has recently included L-DOPA, the generic name for levodihydroxyphenylalanine. The prescribed therapeutic amounts of this drug have been suggested and the resulting circulating blood concentrations documented [*1*]. We have recently observed what appears to be the first death from an overdose of this drug, affording an opportunity to perform distribution studies on the tissues and fluids. Meprobamate and flurazepam (Dalmane) were also recovered, but in trace to therapeutic amounts.

Clinical History

Notification of the death of a husband and wife at their home came from the local police department. The scene revealed a 43-year-old woman lying on her back on the side of a double bed; her husband was in the backyard with a shotgun wound of his chest clearly visible. Although no tablets were found near the bed, available drugs in the medicine cabinet included a full bottle of Dopar and Larodopa, of which thirty-one of a prescribed total of seventy-five 250-mg tablets remained in the bottle. Several letters addressed to the daughters in the husband's handwriting indicated they were "tired and worn out," stated the suggested disposition of their personal property and remains, and one note asked that the treating physician be informed that his wife "blacked out and hit her head" as the Larodopa was "too strong [a] dosage for her." Her recommended daily dose had been recently increased to 6 g per day but she was presently taking 5 g daily in four divided doses. Her medical history dated for several years during which the onset and progressive increase in symptomatology of Parkinson's disease was documented despite increasing dosages of L-DOPA and other medications. Surgical intervention was at one time considered, but not performed.

Autopsy

Autopsy of the wife revealed external bruising of her head, neck, and extremities. These superficial injuries confirmed reports by the husband and neighbors that the woman suffered a number of falls caused by her malady. There was a laceration of the left scalp but no skull fractures or brain injury were observed. The stomach contained 230 g of grumous brown-tan, sour smelling contents. Smaller amounts of similar material were seen in the small intestine. There was terminal aspiration of gastric contents into the air passages. The brain weighed 1260 g and the substantia nigra revealed a decrease in pigmentation. Microscopic studies confirmed the diminution of neurons in this area with abundant pigmentation of the surrounding macrophages. The basal ganglia showed

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moderate degenerative changes. Specimens of tissues and fluids were submitted for toxicologic analysis and it was subsequently concluded that the cause of death was intoxication from L-DOPA ingestion.

Methods for Analysis

L-DOPA (L-dihydroxyphenylalanine)

The method of Sourkes and Murphy [2] was used for the analysis of L-DOPA in 6-g samples of each tissue.

A Fluorispec fluorescence spectrophotometer, Model SF-1, was used for the quantitative determination of L-DOPA. Fluorescence peak heights (λ ex 365, λ fl 485 nm) were found to be reproducible for at least several days so that the same reference solutions could be used from day to day. Recovery of L-DOPA added to tissue homogenates or blood by this procedure was found to be equivalent to recovery from aqueous standard solutions.

Flurazepam (Dalmane)

Samples were extracted with ether, evaporated to dryness, and applied to a thin layer chromatographic plate (silica gel G) along with reference spots of flurazepam and its major metabolite 7-chloro-1-(2-hydroxyethyl)-5-(2-fluorophenyl)-1, 3-dihydro-2H-1,4 benzodiazepin-2-one [3]. The plate was developed with benzene:methanol:acetic acid (90:10:10). The areas of the sample paths on the chromatogram having RF's corresponding to the standards were eluted and examined by gas chromatography. (Conditions for gas chromatographic analysis: instrument HP-5751B; column conditions—6 ft 2 mm inside diameter glass column packed with 3 percent OV-1 on Chromosorb W, 80–100 mesh. Column temperature 240 C; carrier gas, He.)

Hydrolyzed samples were also examined for the benzophenone derivatives of flurazepam and its metabolite by thin layer chromatography [4] and gas chromatography.

Meprobamate

Five ml of blood or 5 ml of gastric content were extracted with 100 ml of chloroform. The chloroform was washed with 0.45*N* NaOH, 0.2*N* H_2SO_4, and 10 ml of H_2O. A tungstic acid protein-free filtrate of 20 g of the liver and kidney was prepared and this filtrate was extracted with 100 ml of chloroform. Each organic layer was evaporated to dryness and then dissolved in 5 ml of chloroform. A 1 to 3 ml aliquot was evaporated to 50 μl and applied to a thin layer chromatographic plate (silica gel G) along with aliquots of reference solutions of meprobamate. The plate was developed in chloroform:acetone (9:1) and sprayed with recently distilled furfural and concentrated hydrochloric acid. Quantitation was accomplished by comparison of the size and intensity of the developed spot with those of the reference solutions.

Results and Discussion

The results of the analyses are summarized in Table 1. L-DOPA was available to the patient in 250 and 500 mg doses. At the time of death her prescribed dose was 5 g per day. The quantity of this drug found in the stomach indicates the recent ingestion of a dose of L-DOPA and the quantities in the blood, liver, and kidney are probably indicative of a partial distribution of this dose. According to Dunner et al [1], a 1000-mg dose of L-DOPA can lead to a plasma concentration of 0.05 mg percent (0.50 μg/ml) with the maximum

concentration occurring 4 h after administration of the last dose. This would suggest that the last dose taken by this patient was more than 1 g. L-DOPA is readily converted in the body to dopamine and other metabolites. The tissue concentrations of this drug may therefore not be indicative of dosage. A brown-tan grumous material found at autopsy in the small intestine was probably the residue from the recently ingested doses of L-DOPA.

TABLE 1—*Results of analysis.*

	L-DOPA	FLURAZEPAM	MEPROBAMATE
Stomach contents	683.0 mg	9.47 mg[a]	3.90 mg
Blood	0.065 mg%	0.0[a]	0.59 mg%
Liver	0.520 mg%	0.0	0.66 mg%
Kidney	0.500 mg%	0.0	0.64 mg%

[a] Analysis through courtesy of Hoffmann-LaRoche, Inc., Nutley, N.J.

No flurazepam could be detected by our analysis in the blood, liver, or kidney. An independent analysis detected 9.47 mg of flurazepam in the stomach and none in the blood. The usual adult dosage of this drug is 15 to 30 mg. Meprobamate was detected in the stomach contents as well as in the blood, liver, and kidney. The blood concentrations of meprobamate after therapeutic doses range from 0.5 to as high as 3.00 mg percent and in fatalities due to meprobamate overdosage, the mean blood concentration is about 22.6 mg percent [5]. The patient was prescribed 400 mg of meprobamate. The analyses indicate that the two drugs (meprobamate and flurazepam) had been taken by the subject at some time prior to death, but in therapeutic or less than therapeutic quantities.

Although the exact quantity of L-DOPA ingested is unknown, it could have been as high as 11 g, which is slightly in excess of twice the prescribed daily dose. Since little is known regarding the toxicity of this drug, especially in combination with other drugs such as meprobamate and flurazepam, it is not proven that the death was due solely to an L-DOPA overdose. However, in view of the history and circumstances, as well as the absence of pathologic findings other than Parkinson's disease, which is not a fatal condition in and of itself, it is believed that L-DOPA intoxication, probably on a cumulative basis, was responsible for her death.

Summary

A case of L-DOPA (levodihydroxyphenylalanine) intoxication involving a young woman using the prescribed drug for advancing Parkinson's disease is presented. Analysis for L-DOPA was performed and concentrations of this drug in selected autopsy specimens are reported. Small amounts of flurazepam and meprobamate were also recovered. This appears to be the first death in which toxicologic analysis for L-DOPA was performed.

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