FEBRILE REACTIONS TO L-ALPHA-METHYL-DOPA

Report of Three Cases

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RECENT studies[1-8] of a new decarboxylase inhibitor, alpha-methyl-dopa (alpha-methyl-3, 4-dihydroxy-L-phenylalanine), have demonstrated its antihypertensive properties. Side effects and toxicity are important aspects to be considered in the evaluation of any new drug. Drowsiness, lethargy, nausea, headache, diarrhea, fluid retention and sexual impotence were noted. In earlier trials with DL-alpha-methyl-dopa, two patients exhibited febrile reactions.[1] To date, there have been no reports of febrile reactions to the L isomer.

During the past 18 months we have treated 50 hypertensive patients with L-alpha-methyl-dopa.† Three patients have exhibited acute febrile illnesses that appear to have been due to the drug.

Report of Cases

Case 1. A 36-year-old unmarried Negro woman was examined on July 12, 1961, because of hypertension of 14 years' duration. Group 2 hypertensive changes were observed in retinal arterioles. Average supine, sitting, and standing blood pressures were 220/127, 218/120, and 206/129 mm. of Hg, respectively. Cardiac and renal functions were normal. Therapy with L-alpha-methyl-dopa, 250 mg. four times daily, was started August 16, 1961. Drowsiness necessitated reduction in dosage to 250 mg. twice daily on August 28. The next day she reported to the Clinic because of myalgia, malaise, chills, nonproductive cough, and headache. Oral temperature was 103.8 F. Physical examination demonstrated no significant abnormalities, and culture of the urine was sterile. Blood pressure supine was 180/80 mm. of Hg, and sitting was 155/70 mm. of Hg. Averages of blood pressure taken at home from August 23 to August 29 were 162/90 mm. of Hg in the sitting position, and 132/86 mm. of Hg in the upright position. Therapy with L-alpha-methyl-dopa was stopped on August 29, and symptomatic therapy was initiated. Within two days she was much improved. For two weeks thereafter the blood pressure remained within normal range without specific antihypertensive therapy.

On September 15, because the diastolic pressure was approaching pretreatment levels, therapy with L-alpha-methyl-dopa was resumed in doses of 250 mg. four times daily. Headache, left flank pain, and oral temperature of 100 F. on two occasions, necessitated re-examination four days later. The oral temperature was normal, and there was tenderness in the left costovertebral angle. Urine culture was sterile. Therapy with L-alpha-methyl-dopa was again stopped. Within two days the patient was much better, but the blood pressure rose again, so the same dosage schedule of L-alpha-methyl-dopa was reinstituted on September 21. Within 24 hours malaise, anorexia, drowsiness, and fever (100 F.) again developed. These symptoms quickly subsided when she stopped taking the drug. Several other antihypertensive agents were subsequently administered to this patient without the appearance of similar symptoms. On January 12, 1962,

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†*Provided as Aldomet in 250-mg. tablets by Merck Sharp & Dohme, West Point, Pennsylvania.*

tests of hepatic function gave the following results: thymol turbidity, 2.5 units; serum bilirubin, 0.4 mg. per 100 ml. direct, with a total of 0.7 mg. per 100 ml.; sulfobromophthalein, 1 per cent retention at 45 minutes; and serum transaminase, 4 units.

Case 2. A 40-year-old Negro man with hypertension of recent onset, was admitted to the hospital August 8, 1961, because of epistaxis. Supine blood pressures were rather labile ranging from 205/145 to 120/88 mm. of Hg. Examination of the optic fundi revealed group 2 arteriolar changes. Cardiac and renal functions were normal. Bleeding was controlled easily with nasal packs. Therapy with L-alpha-methyl-dopa in doses of 250 mg. four times daily was started on August 21. Hydralazine hydrochloride, 10 mg. four times daily, was given from August 25 to August 30. After August 25 treatment was continued on an outpatient basis, the patient recording his own blood pressures at home. On September 8 the daily dosage of L-alpha-methyl-dopa was increased to 1,500 mg. because blood pressure was not ideally controlled. The following day he returned to the Clinic because of pain behind the right ear and the sensation of chilliness. Examination by Dr. Fred R. Tingwald of the Department of Otolaryngology, demonstrated no cause for the pain or the elevation of temperature (102.4 F., orally). A culture of the urine was sterile. The fever and pain abated the next day, and have not recurred despite the continuance of therapy with L-alpha-methyl-dopa in the former dosage of 250 mg. four times daily. Subsequently methyclothiazide* was added to the regimen, and the blood pressure became well controlled within normal range. The results of hepatic function tests performed on January 17, 1962, were: thymol turbidity, 7.2 units; sulfobromophthalein, 19 per cent retention in 45 minutes; serum transaminase, 29 units; and serum bilirubin, 0.4 mg. per 100 ml. direct, with a total of 0.8 mg. per 100 ml. Because of the slightly abnormal thymol turbidity value and the sulfobromophthalein retention, therapy with L-alpha-methyl-dopa was discontinued on February 12, 1962. Hepatic function tests on March 5 gave the following results: thymol turbidity, 5.5 units; sulfobromophthalein, 9 per cent retention at the end of 45 minutes; serum transaminase, 14 units; and serum bilirubin 0.0 mg. per 100 ml. direct, with a total of 1.4 mg. per 100 ml.

Case 3. A 63-year-old white widow was examined on January 16, 1962, because of hypertension of 15 years' duration. Examination revealed cervical osteoarthritis and group 2 hypertensive changes in the retinal arterioles. Average blood pressures in the supine and upright positions were 191/106 and 181/104 mm. of Hg, respectively. Cardiac and renal functions were normal. Trials of therapy with meprobamate,† mebutamate,‡ and methyclothiazide produced no significant hypotensive response. Therapy with L-alpha-methyl-dopa in doses of 250 mg. twice daily was started on February 27 while she continued to receive methyclothiazide, 10 mg. daily. The supine and standing blood pressures were 170/98 and 150/88 mm. of Hg, respectively, on March 6. The patient noted drowsiness during the first two days of therapy with L-alpha-methyl-dopa. On March 14 the patient called up to report fever, malaise, and generalized aching, which had been present for one week. Symptoms subsided within one day after discontinuing therapy with L-alpha-methyl-dopa. Only the methyclothiazide was taken during the ensuing week, and she remained asymptomatic. On the evening of March 20, the day that she resumed taking L-alpha-methyl-dopa, fever, arthralgias, malaise, and vomiting occurred. Treatment with L-alpha-methyl-dopa was stopped and the symptoms subsided promptly. No further trial of treatment with L-alpha-methyl-dopa has been attempted. On March 28 tests of hepatic function gave the following results: alkaline phosphatase, 2.0 Bodansky units; serum transaminase, 22 units; thymol turbidity 5.0 units; and serum bilirubin, 0.4 mg. per 100 ml. direct, with a total of 0.7 mg. per 100 ml.

Enduron, Abbott Laboratories.
†*Equanil, Wyeth Laboratories; Miltown, Wallace Laboratories.*
‡*Capla, Wallace Laboratories.*

Discussion

In cases 1 and 3 there is little doubt that the syndrome described was attributable to therapy with L-alpha-methyl-dopa, for the symptoms abated promptly when therapy was discontinued, and reappeared just as promptly when it was resumed. The evidence for drug fever in case 2 is less convincing, and the fact that symptoms were of short duration and subsided in spite of continuing therapy with L-alpha-methyl-dopa in reduced dosage suggests that this may have been an incidental influenza-like illness. In fact this was our diagnosis in cases 1 and 2 until we discovered that reinstitution of therapy in case 1 was followed by the recurrence of fever.

Gillespie and co-workers[1] reported that one of two patients with a febrile reaction to the DL form of alpha-methyl-dopa had elevated values for serum alkaline phosphatase, serum transaminase, and serum bilirubin. To our knowledge, febrile reactions due to treatment with L-alpha-methyl-dopa (Aldomet) have not been reported previously. Only in case 2 were tests of hepatic function abnormal, and these were made more than four months after the febrile reaction. However, this was the only patient of the three who continued to take L-alpha-methyl-dopa. Unfortunately, pretreatment tests of hepatic function were not obtained. In cases 1 and 3, in which the relationship between therapy with L-alpha-methyl-dopa and the febrile illnesses was well documented, tests for hepatic function gave normal results one week (case 3) and four months (case 1) after it was necessary to discontinue therapy.

It is interesting if not significant that all three of our patients exhibited a good hypotensive response to therapy with L-alpha-methyl-dopa.

Summary

Acute febrile illnesses occurred in three hypertensive patients from 8 to 18 days after starting treatment with L-alpha-methyl-dopa. Prompt subsidence of symptoms when therapy was withdrawn, and recrudescence of symptoms when it was reinitiated seemed to document the role of the drug in the production of the influenza-like syndrome in two cases. In the third case, symptoms subsided after two days despite continuation of treatment with L-alpha-methyl-dopa in reduced dosage. Although similar febrile reactions have been reported previously to therapy with the DL form of alpha-methyl-dopa, this is the first report to our knowledge of this untoward side effect from the L isomer (Aldomet).

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