Clinical and Chemical Studies with \(\alpha\)-Methyl-Dopa in Patients with Hypertension

By Louis Gillespie, Jr., M.D., John A. Oates, M.D., J. Richard Croun, M.D., and Albert Sjoerdsma, M.D., Ph.D.

The biochemical and pharmacologic properties of \(\alpha\)-methyl-3,4-dihydroxy-DL-phenylalanine (DL-\(\alpha\)-methyl-dopa) in man have been described in several reports\(^1\)\(^-\)\(^5\) from this laboratory. These studies showed that, in addition to being a potent inhibitor of the decarboxylation of several aromatic L-amino acids, the compound has sedative and hypotensive properties. Thus, the agent has come to be looked upon as a potentially useful drug as well as an interesting biochemical tool.

The present report covers three phases of additional investigations: (1) further observations were made on the blood pressure lowering effects of the racemic (DL) form of the compound and preliminary data were obtained on its metabolism in man, (2) following resolution of the agent into its D and L isomers, these were tested comparatively and all activity was found to reside in the L-isomer, and (3) studies were initiated to evaluate the usefulness of L-\(\alpha\)-methyl-dopa (Aldomet) as an antihypertensive agent. The conclusion is reached that Aldomet is a promising drug for the treatment of hypertension and has an interesting, albeit incompletely understood, mechanism of action.

Materials and Methods

Clinical

The subjects were 52 patients with persistent primary hypertension; the age range was 32 to 67 years. Complications included: grade III retinopathy, nine cases; grade IV retinopathy, five cases; congestive heart failure, one case; and renal insufficiency with azotemia, four cases. Twenty-eight of the patients were hospitalized and the others were studied as out-patients. All blood pressure measurements were by the arm cuff auscultatory technic. The protocols of individual studies are considered in the appropriate sections.

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blood pressure returned to control levels within a similar interval of time following cessation of treatment.

Blood Pressure Effect in Nonhospitalized Patients. A small pilot study was initiated in nine clinic patients, each of whom had been trained to measure his own blood pressure twice daily, in the recumbent position and after standing for 2 minutes. The severity of hypertension in this group was such as to preclude total withdrawal of antihypertensive medication. Therefore the protocol used included maintenance therapy with chlorothiazide (500 mg. twice daily). In eight patients "control" values were obtained over a 6-week
period of treatment with chlorothiazide plus placebo capsules that were similar in appearance to those containing α-methyl-dopa. In one patient (no. 1, table 1) the control period had to be shortened to 1 week because of a rise in blood pressure resulting in congestive heart failure. The effect of treatment with α-methyl-dopa (plus chlorothiazide) was studied during a separate 6-week period in each case. The order of treatment (placebo vs. α-methyl-dopa) was determined by random selection; six patients received α-methyl-dopa first and three the placebo. The initial dose of α-methyl-dopa was 750 mg. three times daily; this was reduced to 500 mg. three times daily when lowering of blood pressure was excessive.

Average values for blood pressures in the recumbent and standing positions during the final week of control and treatment periods are shown in table 1. A decrease in blood pressure in both positions occurred in all patients during treatment with α-methyl-dopa, the decrease being greatest in subjects with the highest pressures. Several patients also had a lowering of blood pressure in the supine position. The onset of effect was observed within 1 to 3 days, maximal effect being within 2 to 5 days. When treatment with α-methyl-dopa was discontinued, blood pressure values returned to control levels within 2 to 3 days.

Other Effects. A state of drowsiness was noted in all patients during the first 24 to 48 hours of treatment with dl-α-methyl-dopa, with transient recurrence if the dose of medication was increased subsequently. This symptom was most evident in hospitalized patients who frequently slept for long periods. They could be easily aroused, however, and were able to remain awake if occupied. It was our impression that a mild to moderate degree of tranquilization persisted throughout the period of administration of α-methyl-dopa. Infrequent mild complaints of dryness of mouth and decreased sweating were noted but were difficult to evaluate. A moderate slowing of pulse rate was observed consistently, the decrease usually being in the order of 15 to 20 beats per minute. Symptoms of orthostatic hypotension occurred when fall in blood pressure was excessive but there were no syncopal attacks.

Table 1
Effects of dl-α-methyl-dopa on Average Blood Pressure of Nonhospitalized Patients

| Subject no. (age, sex) | Placebo* 
| | mm. Hg | mm. Hg | α-Methyl-Dopa* 
| | Recumbent | Standing | Recumbent | Standing | Change due to α-methyl-dopa 
<table>
<thead>
<tr>
<th></th>
<th>mm. Hg</th>
<th></th>
<th>mm. Hg</th>
<th></th>
<th>mm. Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (58 M)</td>
<td>170/122</td>
<td>144/112</td>
<td>160/112</td>
<td>120/98</td>
<td>−10/10</td>
</tr>
<tr>
<td>3 (48 M)</td>
<td>190/110</td>
<td>170/110</td>
<td>186/100</td>
<td>150/100</td>
<td>−4/10</td>
</tr>
<tr>
<td>4 (46 F)</td>
<td>142/96</td>
<td>142/96</td>
<td>137/95</td>
<td>135/95</td>
<td>−5/1</td>
</tr>
<tr>
<td>5 (50 M)</td>
<td>144/94</td>
<td>154/112</td>
<td>128/80</td>
<td>140/104</td>
<td>−16/14</td>
</tr>
<tr>
<td>6 (46 F)</td>
<td>184/126</td>
<td>194/132</td>
<td>148/92</td>
<td>148/104</td>
<td>−36/34</td>
</tr>
<tr>
<td>7 (53 M)</td>
<td>240/140</td>
<td>246/144</td>
<td>160/108</td>
<td>134/98</td>
<td>−80/32</td>
</tr>
<tr>
<td>8 (57 M)</td>
<td>140/80</td>
<td>176/104</td>
<td>125/75</td>
<td>150/96</td>
<td>−15/5</td>
</tr>
<tr>
<td>9 (38 M)</td>
<td>182/122</td>
<td>182/122</td>
<td>168/110</td>
<td>168/109</td>
<td>−14/12</td>
</tr>
</tbody>
</table>

Average B.P. change for group −27/17 −38/19

*Chlorothiazide, 500 mg. twice daily, was also given during both placebo and α-methyl-dopa periods. Values shown are the averages during final week of treatment; see text for details.
Table 2

Blood Pressure Responses to DL-α-Methyl-dopa Given Intravenously

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Dose (mg.)</th>
<th>Control blood pressure</th>
<th>Maximum decrease</th>
<th>Timing of blood pressure response</th>
</tr>
</thead>
<tbody>
<tr>
<td>(age, sex)</td>
<td>(mg.)</td>
<td>Recumbent mm. Hg</td>
<td>mm. Hg</td>
<td>Onset (hours)</td>
</tr>
<tr>
<td>1</td>
<td>250 + 250</td>
<td>210/120</td>
<td>210/120</td>
<td>no change</td>
</tr>
<tr>
<td>(67 M)</td>
<td>(1 hr. apart)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>210/120</td>
<td>220/120</td>
<td>100/30</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>190/100</td>
<td>210/116</td>
<td>90/40</td>
</tr>
<tr>
<td>2</td>
<td>750</td>
<td>190/110</td>
<td>190/110</td>
<td>90/30</td>
</tr>
<tr>
<td>(43 M)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1000</td>
<td>200/130</td>
<td>190/130</td>
<td>50/20</td>
</tr>
<tr>
<td>(39 M)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>750</td>
<td>210/130</td>
<td>160/128</td>
<td>no change</td>
</tr>
<tr>
<td>(58 M)</td>
<td>1000</td>
<td>236/124</td>
<td>214/120</td>
<td>75/30</td>
</tr>
<tr>
<td>5</td>
<td>400</td>
<td>230/140</td>
<td>220/130</td>
<td>60/40</td>
</tr>
<tr>
<td>(53 M)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1000</td>
<td>164/120</td>
<td>160/116</td>
<td>no change</td>
</tr>
<tr>
<td>(43 M)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1000</td>
<td>210/136</td>
<td>200/136</td>
<td>60/36</td>
</tr>
<tr>
<td>(50 F)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Parenteral Administration

Changes in blood pressure produced by intravenous infusions of DL-α-methyl-dopa are presented in table 2. The doses ranged from 500 to 1,000 mg. except in the case of patient no. 5 who, having diminished renal function (BUN 80 mg. per cent), received only 400 mg. The volumes of the infusions varied from 25 to 100 ml., which were administered over periods of 5 to 15 minutes. As may be seen, lowering of blood pressure in the standing position was observed following seven of the 10 infusions; six of the infusions were followed by a diminution of blood pressure in the recumbent position also. One subject failed to respond to infusion of 1,000 mg. The onset of effect did not occur until 1½ to 4 hours had elapsed following infusion. Maximal effects were observed within 4 to 8 hours after infusion with disappearance of effect in 12 to 24 hours. A representative response is shown in figure 2. Transient drowsiness of varying degree was observed in all cases.

Metabolism

Weissbach et al. have shown that α-methyldopa may be decarboxylated in vitro to α-methyldopamine. Since α-methyldopa and α-methyldopamine are catechols, both these compounds might also be expected to undergo meta-O-methylation to form the correspond-
Example of blood pressure response to DL-α-methyl-dopa intravenously.

Can be assumed as representative of the entire series of patients, the total recovery of urinary metabolites was approximately 15 to 30 per cent of the oral dose. Since chromatography indicated no major metabolite was being overlooked, the inability to recover large portions of the oral dose suggested rather poor absorption of the drug from the gastrointestinal tract.

Two of the above-mentioned patients (A.J. and R.S.) also received intravenous infusions of 1.0 Gm. of the compound in 100 ml. of iso-
tonic saline over a 15-minute period. The total urinary excretion in 24 hours of DL-α-methyl-dopa plus α-methyl-dopamine was 86 per cent and 94 per cent respectively. Alpha-methyl-dopamine accounted for less than 2 per cent of the total recovery. The blood pressure responses in the recumbent and standing positions and plasma levels of DL-α-methyl-dopa following its oral and intravenous administration in patient R.S. are shown in figure 3. Only slight orthostatic lowering of blood pressure and mild drowsiness along with rather low blood levels of the drug resulted from the oral dose. Following the intravenous dose, no effects were noted immediately despite very high plasma levels. After 1 to 2 hours, arterial pressure began to decline and drowsiness appeared. Sedation was maximal at 4 to 5 hours and peak blood pressure effect was at 7 to 8 hours. By this time 90 per cent of the dose had been excreted in the urine and the plasma level of the drug was one fiftieth of its initial value. A less pronounced blood pressure fall and sedative effect occurred in the second patient (A.J.) but the timing of responses was similar.

Comparison of the Two Isomers

It seemed important from both a theoretical and practical point of view to determine whether decarboxylase inhibition and blood pressure lowering in man might be attributable selectively to either the d or L isomer of α-methyl-dopa. Therefore, various forms of the compound were administered orally to three hypertensive subjects to study the effects on amino acid decarboxylation and blood pressure. In two subjects, the urinary excretion of tyramine during an 8-hour period following oral administration of the precursor amino acid, L-tyrosine (10.0 Gm. in vehicle of applesauce), was determined daily during a control period and during administration of the dL, d, and L-α-methyl-dopa, single doses of which were given 2 hours prior to the tyrosine load. Findings in one of these patients are shown in figure 4. Formation of urinary tyramine was markedly inhibited by oral doses of 2.0 Gm. of dL and 1.0 Gm. of L, and perhaps reduced slightly by 2.0 Gm. of d (i.e., twice as much as present in 2.0 Gm. of dL). The average daily standing blood pressure was reduced considerably during dL administration, reduced to the same degree by L, and little if at all affected by d. Similar chemical and pharmacologic effects were noted in the other patient.4

The third patient was studied during treatment with 75 mg. per day of MO-911, a potent monoamine oxidase inhibitor and antihypertensive agent.9 Inhibition of the degradation of endogenously formed tyramine by MO-911 resulted in a rise in the urinary excretion of this amine (fig. 5). It was possible thereby to study the effects of superimposed decarboxylase inhibition on the endogenous production of tyramine. Addition of the dextro

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Table 3

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose (mg.)</th>
<th>24-Hour excretion (mg.)</th>
<th>Total (mg.)</th>
<th>Total excretion as percentage of oral dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>α-methyl-dopa</td>
<td>α-methyl-dopamine</td>
<td></td>
</tr>
<tr>
<td>R.E.</td>
<td>1000</td>
<td>129</td>
<td>3</td>
<td>132</td>
</tr>
<tr>
<td></td>
<td>1000</td>
<td>180</td>
<td>12</td>
<td>192</td>
</tr>
<tr>
<td>E.C.</td>
<td>2000</td>
<td>208</td>
<td>6</td>
<td>214</td>
</tr>
<tr>
<td></td>
<td>2000</td>
<td>338</td>
<td>8</td>
<td>346</td>
</tr>
<tr>
<td>A.J.</td>
<td>1000</td>
<td>115</td>
<td>6</td>
<td>121</td>
</tr>
<tr>
<td></td>
<td>1000</td>
<td>..</td>
<td>..</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>3000</td>
<td>..</td>
<td>..</td>
<td>527</td>
</tr>
<tr>
<td>R.S.</td>
<td>1000</td>
<td>67</td>
<td>3</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>1000</td>
<td>..</td>
<td>..</td>
<td>188</td>
</tr>
<tr>
<td>W.C.</td>
<td>4500</td>
<td>..</td>
<td>..</td>
<td>790</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Average</td>
</tr>
</tbody>
</table>
isomer (3.0 Gm. daily in divided doses) resulted in no significant change in tyramine excretion. However, administration of the levo form (750 to 1,250 mg. daily in divided doses) resulted in immediate lowering of urinary tyramine levels to within the control range. In the course of this study, the blood pressure, already decreased initially in the standing position by MO-911, fell to even lower levels with the addition of the levo form, but was not affected by administration of the dextro isomer.

From studies of this type, it was concluded that the levo isomer possesses essentially all of the decarboxylase inhibiting property as well as the ability to lower blood pressure. By use of the levo form of \(\alpha\)-methyl-dopa, it was possible to reduce dose requirements in hypertensive patients by at least one half.

**Clinic Study of L-\(\alpha\)-Methyl-Dopa (Aldomet)**

After demonstrating that the pharmacologic and chemical activity in man resides in the levo isomer, another clinic study was instituted to evaluate the possible long-term effectiveness of the L-isomer, referred to hereafter as Aldomet. To the time of this writing, 20 hypertensive patients have entered the study, five having previously participated in evaluation of the DL-compound. All patients had diastolic blood pressure levels above 110 mm. Hg in both recumbent and standing positions. We were interested chiefly in how well the compound would be tolerated on a chronic basis and the ease with which effective blood pressure control could be maintained. Aldomet was administered alone in eight cases in a dosage range of 0.75 to 3.0 Gm. daily in two or three divided doses. In the remaining 12 cases Aldomet was administered at the same levels of dosage but in combination with chlorothiazide, 500 mg. twice daily. Eleven patients recorded their own blood pressures at home in each position; nine patients had their pressures recorded during frequent clinic visits.

While this study group is still being enlarged and further observations are required, a few preliminary statements seem warranted. Reduction of standing diastolic levels to less than 100 mm. Hg was achieved rapidly and

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**Figure 3**

Pharmacologic effects and plasma levels of DL-\(\alpha\)-methyl-dopa following its oral and intravenous administration. Scale of drowsiness is arbitrary, sleep equaling 4+. 
has been maintained in 18 patients in this group during treatment periods of 3 to 9 months. Several patients have also had significant decreases in blood pressure in the recumbent position. During the fourth week of therapy, two patients requested that the drug be discontinued because of persistent sedation that was considered intolerable. There has been no indication of development of tolerance to the drug. One patient in this group was a 44-year-old woman whose blood pressure had been controlled on the parent compound and chlorothiazide for 11 months prior to switching to Aldomet and chlorothiazide. She has now been on the latter combination for an additional 12 months. Thus, consecutive administration of L-a-methyl-dopa for 23 months in combination with chlorothiazide represents the longest duration of therapy with this drug, producing satisfactory control of blood pressure without adverse effects.

Summary of Undesirable Side Effects

Thirty additional patients with various disorders have received L-a-methyl-dopa (either DL or L forms) during metabolic and therapeutic studies, making a total of about 80 subjects in whom the effects of this agent have been observed. No prohibitive side effects have occurred with the use of Aldomet, with the exception of two cases of excessive sedation as mentioned above. We have recently encountered one instance of sexual impotence in a young male hypertensive receiving Aldomet.

Reactions that were cause for serious concern have occurred thus far only with DL-a-methyl-dopa and include the following: (1) three cases of psychic depression, all quickly reversible and (2) two febrile reactions, one of which was associated with transient abnormalities in liver function.

Agitated depression, which included inability to sleep and expression of suicidal thoughts, occurred in two patients within 48 hours of beginning therapy with DL-a-methyl-dopa. The drug was discontinued promptly and all depressive symptoms disappeared within 24 hours. One of these patients was a known manic-depressive individual and the...
other had had a depressive reaction to reserpine. The third depressive reaction, occurring in a 62-year-old woman, developed over a period of 3 weeks and consisted of diminishing self-motivation with increasing apathy and tendency to weep. These symptoms culminated in an episode of thickened, slurred speech unassociated with localizing neurologic signs. All findings disappeared within 24 hours after discontinuation of therapy. This patient had a previous history of a depressive psychosis while receiving Rauwolfia alkaloids, requiring hospitalization.

The two febrile reactions occurred during early clinical trials with Dl-a-methyl-dopa. In one patient, a 55-year-old hypertensive man, administration of the drug (2.0 to 4.0 Gm. per day) on each of three separate occasions resulted within 1 to 3 days in fever up to 40 C. There were no associated subjective symptoms other than mild malaise, no positive physical findings, and extensive laboratory tests yielded negative results. In the second case, a 47-year-old hypertensive man with a prior history of drug allergy, no abnormalities appeared until the twelfth day of therapy, at which time fever (39.5 C.) occurred in association with elevations of serum alkaline phosphatase, transaminase, and bilirubin. Coincidentally, there was tenderness in the right upper abdominal quadrant though the liver could not be palpated. Circulating eosinophils, noted to be elevated prior to therapy, rose to higher levels but there was no leukocytosis. All abnormalities cleared within 5 days after stopping the drug. A punch biopsy of the liver performed 1 week after the onset of fever yielded only normal hepatic tissue. Similar abnormalities in liver function, but without other signs and symptoms, recurred upon subsequent administration of the dl-drug for 2 days.

Discussion

From studies to date, it seems likely that a-methyl-dopa has a potentially broader range of application as an antihypertensive than other drugs in current use. Mild hypertension is easily managed with the drug alone but, in addition, it is usually effective in severe hypertension, alone or with chlorothiazide. Its use parenterally affords another means of controlling hypertensive crises. Other favorable properties of the drug are the smoothness of its action and its frequent effect of lowering both recumbent and standing blood pressure. Its mild sedative and tranquilizing properties should be of particular benefit to the hyperactive patient.

The two major considerations regarding the eventual outlook for use of the drug as an antihypertensive appear to be (1) incidence of toxic effects and (2) the frequency with which tolerance develops. Patients with a history of psychic depression should be followed carefully, particularly during the first few days of treatment. Fortunately, from experience cited here in three cases of depressive reactions, it appears that rapid reversal occurs when the drug is discontinued. Whether febrile reactions or hepatic toxicity, as noted here with Dl-a-methyl-dopa, will also occur with Aldomet is unknown. There has been no clear indication of tolerance in patients studied thus far. Once the antihypertensive effect is established, it appears to be maintained. Though the responsiveness of individual patients is quite variable, the percentage of nonresponders is probably small.

The mechanism by which a-methyl-dopa lowers blood pressure is incompletely understood at present. In spite of the demonstration that the compound inhibits synthesis of certain vasoactive aromatic amines from their corresponding amino acids in man, there is at this time some doubt that a cause-and-effect relationship exists between blood pressure lowering and decarboxylase inhibition. Indeed, definitive studies in man to support such a relationship remain to be performed. What effects moderate degrees of alteration of norepinephrine synthesis might have on blood pressure regulation in man as carried out by the sympathetic nervous system would be difficult to assess at best. Rate of synthesis of norepinephrine, its degree of accumulation in stores, and its rate of release at end-organ sites are all variables, each or several of which may be altered by drugs now known
to reduce sympathetic activity and result in a lowering of the blood pressure. Such considerations make it impossible to draw any final conclusions from such observations in man as the time lapse between peak plasma levels of α-methyl-dopa and reduction in the blood pressure. Indeed, such data are quite parallel to those obtained with the parenteral admistration of Rauwolfia alkaloids, which are known to bring about release of norepinephrine from storage depots.

Biochemical studies in laboratory animals by Hess and associates10 in the National Heart Institute and Porter et al.11 at the Merck, Sharp and Dohme Laboratories may afford an explanation for the hypotensive effects of this drug. Since the blood pressure effects in man resembled those produced by sympathectomy, both groups focused their attention on tissue levels of norepinephrine following single injections of α-methyl-dopa and an analogue, α-methyl-meta-tyrosine. Marked depletion of norepinephrine from brain and peripheral tissues was found. Depletion of this amine persisted for several days beyond the period of decarboxylase inhibition (which lasted only a matter of hours) and was present at a time when biosynthetic mechanisms and tissue levels of the norepinephrine precursor (dopamine) were found to be normal. It remains to be determined whether α-methyl-dopa, an amino acid itself, or one of its metabolites (such as α-methyl-dopamine) is primarily responsible for this tissue depletion. Porter et al. have also found that α-methyl-dopamine, shown here to be a significant metabolite in man, is somewhat more effective as a depleting agent than its parent amino acid. Finally, Hess and associates conclude from their work that the effect on norepinephrine is due to impairment of tissue-binding mechanisms.

We have recently obtained more direct preliminary evidence that decarboxylase inhibition is perhaps not a basis for blood pressure reduction in man. Using two other decarboxylase inhibitors, α-methyl-5-hydroxytryptophan given intravenously and the hydrazino analogue of α-methyl-dopa (MK-485, Merck, Sharp and Dohme) given orally, we have produced marked inhibition of decarboxylation in hypertensive patients without sedation or alterations in blood pressure. Therefore, it should also be noted that we have observed a hypotensive response in patients only with inhibitors of decarboxylation which have concomitantly produced sedative effects. Such a preliminary observation may indicate that the site of action of α-methyl-dopa or one of its metabolites lies within the central nervous system.

Thus, it is tempting at the present time to relate the blood pressure effects of α-methyl-dopa in man to depletion of norepinephrine in the brain or sympathetic nerves, or both, peripherally. Nevertheless, in our opinion it is still premature to accept this apparently logical explanation without reservation. Unlike the situation with other norepinephrine-depleting agents such as reserpine and guanethidine, it has not been possible to demonstrate sympathetic blockade in the dog with α-methyl-dopa12 and, indeed, lowering of blood pressure has been unimpressive in various animal preparations except in the renal hypertensive rat. Also, the frequency of blood pressure responses observed in the recumbent position in man implies an added action different from that of the known selective blockers of sympathetic transmission.

Summary

A series of observations in 52 hypertensive patients is presented indicating that α-methyl-dopa is an effective antihypertensive agent.

The antihypertensive properties of the agent were discovered in the course of biochemical studies with the racemic compound, the form used in initial therapeutic trials.

Studies on metabolism of DL-α-methyl-dopa indicate incomplete intestinal absorption and rapid excretion in the urine as unchanged drug and as α-methyl-dopamine. The former finding does not seem to be a significant deterrent to its use orally.

Comparisons of the D and L isomers of α-methyl-dopa in hypertensive patients showed

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that all the chemical and pharmacologic
effects reside in the L-isomer (Aldomet). Thus,
recent studies have been performed with
Aldomet exclusively.

From observations to date the impres-
sion has been gained that Aldomet has
several advantages over other antihyperten-
sive agents; these include effectiveness against
all degrees of hypertension, frequent lowering of
recumbent as well as standing blood pres-
sure, smoothness of effect, and tranquilizing
effects. Questions of toxicity and tolerance
are not yet completely answered.

Sympathetic blockade at a central or pe-
ripheral site is the probable basis of the drug's
action. This effect may be unrelated to the
biochemical property of inhibiting the decar-
boxylation of aromatic L-amino acids and is
possibly due to depletion of tissue stores
of norepinephrine by a mechanism not yet
fully defined.

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