Drug Therapy of Hypertension*

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During the past 15 years, a succession of antihypertensive drugs has been introduced for clinical use. The wide spectrum of available agents has resulted inevitably in changing therapeutic approaches to the management of diastolic hypertension. The adrenergic and ganglion blocking compounds have been largely supplanted by newer agents; and the use of rauwolfia, veratrum, and hydralazine has declined. In contrast, there has been an increasing usage of oral diuretics and sympatholegic drugs which affect catecholamine metabolism. It is the purpose of this paper to review the clinical status of the various antihypertensive drug groups and to outline an overall approach to the management of the ambulatory patient with diastolic hypertension.

Oral Diuretics. Of the various antihypertensive drug groups which are currently available, the oral diuretics probably have the greatest overall clinical usefulness. Their therapeutic advantages may be summarized as follows. First, these agents exert substantial individual antihypertensive actions. Secondly, they lower blood pressures both in the supine and erect positions. Third, the overall incidence of side reactions accompanying their usage is low. Fourth, their antihypertensive effects are maintained despite prolonged administration. Finally, the oral diuretics act to potentiate or enhance the effectiveness of all the other available hypotensive agents. Thus, the combination of diuretic drugs with other antihypertensive compounds frequently will accomplish the desired antihypertensive response in patients who fail to respond to diuretic therapy alone.

The oral thiazide, phthalimidine, and quinazoline diuretics are particularly suited to the long-term treatment of hypertension. It is noteworthy that all of the currently available drug members of these three groups have similar diuretic and natriuretic potencies. Therefore, despite differences in milligram potency, similar antihypertensive responses are obtained when maximum or equivalent dosages of these agents are employed (Table 1).

Approximately 50 per cent of patients treated with chlorothiazide, hydrochlorothiazide, flumethiazide, or hydroflumethiazide obtain significant blood pressure reduction. The usual dosages employed are 100 mg. daily of chlorothiazide (Diuril) or flumethiazide (Ademol) and 100 mg. per day of hydrochlorothiazide (Esidrix, Hydrodiuril, Oretic) or hydroflumethiazide (Saluron). Equivalent dosages of other

<table>
<thead>
<tr>
<th>Drug Regimen</th>
<th>Supine</th>
<th>Mean Blood Pressure Reduced&gt;20 mm.Hg or Normotensive No.</th>
<th>Mean Blood Pressure Reduced&gt;20 mm.Hg or Normotensive No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorothiazide**</td>
<td>50</td>
<td>9</td>
<td>18</td>
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<tr>
<td>Hydrochlorothiazide</td>
<td>54</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>Flumethiazide**</td>
<td>17</td>
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<td>12</td>
</tr>
<tr>
<td>Quinethazone††</td>
<td>29</td>
<td>5</td>
<td>17</td>
</tr>
</tbody>
</table>

*Blood pressure reduced to 140/90 mm.Hg or less; **500 mg. B.I.D.; †50 mg. B.I.D.; ††100-200 mg. daily
thiazide diuretics produce similar antihypertensive results.

The phthalimidine and quinazoline compounds, like the benzothiadiazine drugs, are potent diuretic agents which are well tolerated orally. The antihypertensive effectiveness of chlorthalidone (a phthalimidine) and quinethazone (a quinazoline) is similar to that achieved with the thiazide drugs. In comparison with chlorothiazide, both chlorthalidone (Hygroton) and quinethazone (Hydromox) have similar diuretic potencies, but more prolonged duration of activity. That is, whereas the diuretic effect of chlorothiazide is generally spent within 12 to 18 hours, the action of quinethazone is prolonged for approximately 24 hours and the effect of chlorthalidone may persist for 48 hours or more. Both chlorthalidone and quinethazone are employed usually in dosages of 100 mg per day.

**Rauwolfia.** During recent years, several investigations have suggested that the rauwolfia alkaloids have extremely limited or no antihypertensive action and that their clinical application should be dismissed. In contrast, our own studies indicate that whereas the rauwolfia compounds have only modest antihypertensive effectiveness, they are nonetheless active and do in fact possess certain therapeutic advantages. Their clinical usefulness may be summarized as follows. First, in those instances in which an antihypertensive response is obtained with rauwolfia, both the supine and erect blood pressures are lowered. Secondly, rauwolfia exerts a mild sedative effect which may be beneficial in those hypertensive subjects who are tense and anxious. Third, their bradycrotic action may offer particular therapeutic benefit in certain cases. Finally, the rauwolfia drugs also enhance the effectiveness of other antihypertensive agents; and they are especially useful in combination with thiazide diuretics, hydralazine, and veratrum.

Numerous rauwolfia compounds are currently available including the single pure alkaloids of rauwolfia serpentina (reserpine, rescinnamine and deserpine), various preparations containing multiple active alkaloids (alseroxylon and whole root), and synthetic reserpine-like analogues (syrosingopine). Although there is statistically little difference in the antihypertensive response obtained with these various derivatives, the incidence of associated side effects appears to be least with the alseroxylon fraction (Rauwiloid), the whole root (Raudixin), and syrosingopine (Singoserp).

When rauwolfia is administered orally, a minimum period of two to three weeks is required before maximum therapeutic effectiveness is achieved. It is recommended therefore that an initial loading dose of 8 mg of alseroxylon, 200 mg whole root, 0.5 mg reserpine, or 4 mg. syrosingopine be given during the first two weeks of treatment. Thereafter, the dosage should be reduced in half for maintenance therapy.

**Hydralazine.** Hydralazine (Apresoline) possesses moderate antihypertensive potency, somewhat greater than that of the rauwolfia alkaloids, but generally less than that achieved with the oral diuretics. The major untoward reactions observed with hydralazine are related to the cardiostimulatory actions of the compound. These latter effects may aggravate coronary insufficiency, and actual instances of myocardial infarction have been precipitated. For this reason, hydralazine is preferably avoided in patients with angina pectoris or other evidences of dynamic coronary artery disease. Likewise the drug probably should never be used as the sole antihypertensive agent. Instead it is advantageous to use hydralazine in combination with other hypotensive compounds, especially the oral diuretics, rauwolfia or guanethidine. The latter two agents have bradycrotic actions which tend to lessen the cardiostimulatory effects of hydralazine.

The recommended initial dosage is 100 mg daily (25 mg q.i.d.). Thereafter, the daily dosage of hydralazine may be doubled at weekly intervals until an adequate reduction of blood pressure has been accomplished or else the incidence of side effects becomes prohibitive. In order to achieve
optimum results, it is mandatory that drug dosage titration be carried out; in addition, because of its short duration of action (four to six hours), hydralazine should be administered at least three or preferably four times daily. Total daily dosage generally should not exceed 400 mg. (100 mg. q.i.d.), since the use of larger doses may be associated with the development of a mesenchymal lupus erythematosus-like syndrome. Although uncommon, a few case reports of iatrogenic lupus have been reported in the patients receiving as little as 100 mg. per day.

*Veratrum.* The veratrum plants contain numerous alkaloids with similar actions, but different potencies. Alkavervir (Veriloid) and protoveratrine (Veralba) are the two most important veratrum compounds in use today. Alkavervir is a purified extract of veratrum viride, and protoveratrine is a mixture of protoveratrine A and protoveratrine B, derived from veratrum album.

All currently available veratrum preparations exert emetic effects which are central in origin. The margin between hypotensive and emetic dosage is narrow. Hence the use of veratrum drugs alone is of limited clinical value. On the other hand, the concomitant administration of other antihypertensive agents, especially the oral diuretics and rauwolfia compounds, lessen the veratrum dosage requirement and thereby decrease the incidence of accompanying side reactions. For this reason, veratrum drugs should be used generally in combination with other antihypertensive agents.

*Ganglion Blocking Agents.* With the availability of guanethidine and newer antihypertensive drugs which affect catecholamine metabolism, the clinical indications for ganglioplegic drug therapy have lessened. Nonetheless these compounds remain among the most potent antihypertensive drugs available, and hence they continue to offer clinical usefulness in certain patients resistant to other hypotensive agents. Multiple preparations are available including pentolinium (Ansolysen), chlorisondamine (Ecolid), and mecamylamine (Inversine). The approximate equivalent dosages of these drugs are 20 mg. pentolinium, 12.5 mg. chlorisondamine, and 2.5 mg. mecamylamine. Determination of optimum drug dosage is dependent upon effective drug dosage titration. Mecamylamine appears to be the ganglioplegic drug of choice, primarily because of its absorption from the gastrointestinal tract is complete. Therefore, the daily hypotensive response is more nearly uniform than that achieved with the other ganglion blocking compounds.

The side reactions encountered with ganglion blocking agents are predominantly parasympatholytic in type. However, the incidence of side effects differs with the various drugs. Constipation and dryness of the mouth are more frequent and of greater severity following the administration of mecamylamine, whereas blurring of vision and photophobia are more severe with chlorisondamine. Thus, it may be helpful to shift to a different ganglion blocking drug if a particular side effect is too severe or cannot be otherwise controlled.

*Guanethidine.* Guanethidine (Ismelin) possesses antihypertensive potency similar to that of the ganglion blocking compounds. In contrast with the ganglioplegic drugs, guanethidine administration is accompanied by a lesser incidence of side reactions, lack of parasympatholytic effects, and a more prolonged duration of action (thereby requiring drug usage only once or twice daily). On the other hand, predominant orthostatic blood pressure reduction is obtained with guanethidine, as with the ganglioplegic drugs. The only untoward reactions of consequence are diarrhea and failure of ejaculation. The diarrhea manifests itself as frequency of bowel habit (three to five times daily) rather than loose stools and, if necessary, can be improved with anticholinergic drugs.

In order to achieve maximum antihypertensive results with guanethidine, careful dosage titration is required. The drug is started usually in dosages of 20 to 25 mg.
daily and then increased by 10 mg. increments at seven to 14 day intervals, until a significant antihypertensive response has been achieved. The hypotensive effect is delayed for two to three days following oral administration, but the ensuing blood pressure reduction is prolonged (for seven to 14 days) once an effective response has been obtained. The concomitant administration of oral diuretics lessens the dosage requirement of guanethidine, improves the supine response, and reduces the incidence of accompanying side reactions.

Methyl Dopa (Methyl Dihydroxyphenyl Alanine). Methyl dopa (Aldomet) is a decarboxylase inhibitor which interferes with the biosynthesis of norepinephrine (Fig. 1). Numerous clinical studies have confirmed the antihypertensive effectiveness of methyl dopa in hypertensive patients, and it has been further demonstrated that the hypotensive effect is potentiated by the concomitant administration of diuretic agents. The incidence of accompanying

<table>
<thead>
<tr>
<th>Drug Regimen</th>
<th>No. of Patients</th>
<th>Normotenive No.</th>
<th>Supine Mean Blood Pressure Reduced &gt;20 mm.Hg or Normotenive No.</th>
<th>Erect Mean Blood Pressure Reduced &gt;20 mm.Hg or Normotenive No.</th>
<th>Per Cent</th>
<th>Per Cent</th>
<th>Per Cent</th>
<th>Per Cent</th>
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<tr>
<td>Pargyline</td>
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<td>15</td>
<td>7</td>
<td>21</td>
<td>17</td>
<td>52</td>
<td>27</td>
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<td>Pargyline plus hydrochlorothiazide</td>
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<td>1</td>
<td>9</td>
<td>4</td>
<td>36</td>
<td>2</td>
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<tr>
<td>Methyl dopa</td>
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<td>16</td>
<td>13</td>
<td>34</td>
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<td>56</td>
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NOREPINEPHRINE METABOLISM

Tyrosine

\[ \text{Dopa} \]

\[ \text{DOPA DECARBOXYLASE} \]

\[ \text{Dopamine} \]

\[ \text{NOREPINEPHRINE} \]

\[ \text{MONOAMINE OXIDASE} \]

\[ \text{Normetanephrine} \]

\[ 3,4 \text{ Dihydroxymandelic acid} \]

\[ \text{MONOAMINE OXIDASE} \]

\[ 3\text{-Methoxy, 4-Hydroxy-mandelic acid} \ (\text{VMA}) \]

FIGURE 1: Dopa decarboxylase catalyzes the conversion of dopa to dopamine, whereas monoamine oxidase is active in the degradation of norepinephrine.

<table>
<thead>
<tr>
<th>Table 3—Comprehensive Therapeutic Regimen</th>
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<tbody>
<tr>
<td>Severity of Hypertension</td>
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<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
</tr>
<tr>
<td>&gt;90 mm.Hg but &lt;110 mm.Hg</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
</tr>
<tr>
<td>&gt;110 mm.Hg but &lt;130 mm.Hg</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
</tr>
<tr>
<td>&gt;130 mm.Hg</td>
</tr>
</tbody>
</table>

*May use other thiazide or phthalimidine or quinazoline diuretics with equally good results.
side reactions is low; most commonly encountered are transient drowsiness, dry mouth, nausea and nightmares. Although the drug does exert both supine and orthostatic antihypertensive effects, it is noteworthy that a greater orthostatic response is generally obtained. Nonetheless, the disparity between supine and orthostatic effect is not as prominent as that obtained with guanethidine or ganglion blocking drugs.

In order to achieve optimum results, drug dosage titration is required. The usual starting dosage is 500 mg. daily; then the dose may be increased by 250 mg. increments, at weekly or bi-weekly intervals, until the desired antihypertensive response is obtained.

As an overall appraisal, it does appear that the decarboxylase inhibitor, methyl dopa, possesses substantial antihypertensive effectiveness. The drug is, however, less potent than guanethidine and the ganglion blocking drugs (Table 2). Its ability to reduce consistently renal vascular resistance suggests particular usefulness in hypertensive patients with renal functional impairment and in subjects with renal hypertension.

Pargyline. Pargyline (Eutonyl), the newest addition to the antihypertensive drug armamentarium, is a monoamine oxidase (MAO) inhibitor. Although other MAO inhibitors have demonstrated antihypertensive effects, only pargyline thus far has demonstrated sufficient potency to be therapeutically applicable to the usual hypertensive situation. Despite its recent introduction to the current antihypertensive drug armamentarium, pargyline has undergone considerable clinical investigation. The clinical results obtained to date indicate that this drug has antihypertensive potency equivalent to that of guanethidine and the ganglion blocking agents (Table 2).

Pargyline, like guanethidine and the ganglio-plegic drugs, exerts a predominant orthostatic antihypertensive effect.\(^\text{19}\) As with the latter agents, the addition of an oral diuretic enhances the antihypertensive response and diminishes the dosage requirement of pargyline. The most prominent side reactions are dry mouth, insomnia, daytime drowsiness, nervousness, weight gain, and impotence or inability to ejaculate. However, at times, pargyline may exert a euphoric action which may be helpful in depressed hypertensive subjects.

At present, it would appear that pargyline will have its greatest usefulness (as do guanethidine and the ganglio-plegic drugs) in the treatment of patients with the more severe degrees of diastolic blood pressure elevation. The usual starting dosage of pargyline is 10 to 25 mg. daily. The onset of action is slow (three to four days) and is cumulative for a seven to 14 day interval. Therefore drug dosage should be increased slowly by 10 mg. increments at weekly or preferably bi-weekly intervals, until the desired antihypertensive response is obtained.

Comprehensive Therapeutic Regimen

An overall therapeutic regimen for the ambulatory patient with diastolic hypertension is outlined in Table 3. It is recommended that one of the thiazide (or phthal-imidine or quinazoline) diuretics be utilized as basic therapeutic agents, because of their (1) individual antihypertensive attributes and (2) ability to potentiate all of the other available antihypertensive drugs. If the oral diuretic fails to achieve the desired response, a rauwolfia drug should be added to the therapeutic regimen after two weeks. Thereafter, if the blood pressure remains elevated after two or more weeks of combination therapy, hydralazine or a veratrum compound should be given in addition. Patients with moderate diastolic blood pressure elevation generally require a combination of an oral diuretic plus rauwolfia or methyl dopa. In those instances of severe or rapidly progressive hypertension, it is recommended that guanethidine or pargyline be added to the therapeutic regimen without delay. Most patients with moderate or severe diastolic hypertension require a double or triple-
drug regimen in order to accomplish significant blood pressure reduction.

**SUMMARY**

With the currently available antihypertensive drug armamentarium, it is possible to control diastolic hypertension in the overwhelming majority of hypertensive patients. In order to accomplish a normotensive result, however, a double or triple drug regimen is often required. The ultimate goal of the therapist will not be accomplished until the mechanisms underlying the etiology of essential hypertension are fully elucidated.

**Resumen**

Con las drogas disponibles como antihipertensoras es posible controlar la hipertensión diastólica de la inmensa mayoría de los casos de hipertensión. Para obtener un nivel normotenso, sin embargo, se requiere un régimen triple de drogas, a menudo. El objetivo final del tratamiento no se obtendrá sino hasta que los mecanismos etiológicos de la hipertensión esencial sean completamente aclarados.

**Résumé**

Avec l'armement thérapeutique anti-hypertensif qui est à notre disposition, il est possible de lutter contre l'hypertension diastolique dans la grande majorité des malades hypertendus. Toutefois, pour obtenir une tension normale il est souvent nécessaire de faire appel à la combinaison de deux ou trois traitements. Le but final du thérapeute ne sera pas atteint tant que n'auront pas été éclaircées d'une façon totale tous les médicaments qui sont à l'origine de l'hypertension essentielle.

**Zusammenfassung**

Mit dem augenblicklich zur Verfügung stehenden medikamentösen antihypertonischen Rüstzeug ist es möglich, die diastolische Hypertonie in der überwiegenden Mehrzahl von Patienten mit Hypertonie zu bekämpfen. Um das Ziel eines normalen Druckes zu erreichen, ist jedoch oft eine Anwendung von zwei oder 3 Medikamenten erforderlich. Das schliessliche Ziel des Therapeuten wird nicht eher erreicht, ehe nicht die Mechanismen, die der Aetiologie der essentiellen Hypertonie zugrundeliegen, in vollem Umfang ans Licht gebracht worden sind.

**References**


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