Side Effects of Sympatholytic Antihypertensive Drugs

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SUMMARY Antihypertensive drugs with pharmacological action due to sympatholytic activity have been second only to diuretics in their use and efficacy in normalizing blood pressure. Their pharmacological actions have resulted in the notable absence of chemical toxicity, but because of symptomatic side effects, their use has been limited relative to some of the newer antihypertensive agents. Most prominent among undesirable side effects are the central nervous system findings of sedation, altered thought process, depression, and orthostatic or exercise hypotension. Sexual problems, especially in men, are also prominent. Special toxicity is discussed with reference to methyldopa, clonidine, monoamine oxidase inhibitors, and metyrosine. (Hypertension 11 [Suppl II]: II-30–II-33, 1988)

KEY WORDS • methyldopa • reserpine • guanethidine • ganglionic blockers • metyrosine • monoamine oxidase inhibitors • clonidine • guanabenz • guanfacin

Historical Perspective

BEFORE discussing adverse side effects of sympatholytic antihypertensive drugs, it is important to place the role of these important antihypertensive agents in perspective. Among all effective antihypertensive drugs, those reducing blood pressure by interfering with sympathetic outflow are among the first antihypertensive agents to be introduced in humans. Even before introduction of the oral diuretics, a mainstay of antihypertensive therapy, sympatholytic agents were known to reduce blood pressure, though the price of single drug therapy with the then available drugs was a significant symptomatic morbidity. Nonetheless, because antihypertensive therapy was only initiated in the most seriously hypertensive patients, usually those who had already suffered adverse consequences of their long-standing, markedly elevated blood pressure, this symptomatic toxicity was balanced against the precarious clinical state of the patient.

An active agent from the root of the climbing shrub Rauwolfia serpentina was used in ancient Hindu medicine, and it was in 1931 that it was first described in the modern Indian literature to have active psychotropic and antihypertensive effects. Because this observation was not widely known in the Western medical literature, this drug was not introduced into common use for either its psychotropic or cardiovascular effects until the middle 1950s. A decade earlier, α-adrenergic blockers, including phenoxymethylamine, dibenamine, phentolamine, and tolazoline, had been tested for their antihypertensive effects on the premise that excess sympathetic tone with increased norepinephrine release was a probable cause of increased blood pressure. Unfortunately, these drugs had little efficacy in patients with essential hypertension, although they proved to be effective in controlling the increased blood pressure of patients with pheochromocytoma. Also introduced in the 1940s were drugs that inhibited transmission through the peripheral autonomic ganglia. These ganglionic blockers were remarkably effective in reducing blood pressure in the standing position but were relatively ineffective in the supine position. This deficiency, coupled with multiple adverse symptomatic side effects, has essentially eliminated these drugs from use as antihypertensive agents today, although they were the basis of antihypertensive therapy in the 1940s and 1950s. In 1960, a new class of antihypertensive agents was introduced with the discovery that α-methyldopa produced significant antihypertensive effects. Initially developed as a potential antihypertensive agent on the premise that the drug would reduce norepinephrine synthesis since it was an in vitro inhibitor of dopa-decarboxylase, the drug was shown subsequently to be active only centrally and only after it had undergone decarboxylation. It was not an effective inhibitor of catecholamine synthesis because it was later shown that tyrosine hydroxylase, not dopa-decarboxylase, was the rate-limiting step in norepinephrine synthesis. It is now understood that methyldopa and subsequently introduced agents with similar modes of action (clonidine, guanabenz, etc.)
reduce blood pressure by stimulating central adrenergic inhibitory pathways. Depletion of norepinephrine from peripheral adrenergic endings also reduces blood pressure as demonstrated by the efficacy of drugs such as guanethidine. Specific blockers of peripheral α- and β-adrenergic receptors also reduce the effects of sympathetic tone and are effective antihypertensive agents. Finally, inhibitors of catecholamine synthesis are only occasionally effective in essential hypertension, although they are very effective in controlling the hypertension of patients with pheochromocytoma.5 The receptor blocking drugs will be dealt with in greater detail in another portion of the monograph and will not be discussed further here. A schematic outline of the classes of sympatholytic agents and prominent examples of each is shown in Table 1.

Table 1. Sympatholytic Antihypertensive Drugs: Pharmacological Action

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
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| I. Autonomic ganglionic blockade | A. Hexamethonium  
B. Pentolinium  
C. Mecamylamine  
D. Trimethaphan |
| II. Central adrenergic inhibition | A. Methyldopa  
B. Clonidine  
C. Guanabenz  
D. Guanfacin |
| III. Peripheral adrenergic nerve inhibition | A. Guanethidine  
B. Guanadrel |
| IV. Mixed central and peripheral adrenergic inhibition | A. Reserpine (Rauwolfia serpentina)  
B. Monoamine oxidase inhibitors  
1. Pargyline  
2. Phenelzine  
3. Tranexamic acid  
4. Parnate |
| V. Adrenergic receptor blockade | A. Beta: propranolol, metoprolol, atenolol, pindolol, etc.  
B. Alpha: phentolamine, phenoxybenzamine, prazosin, etc.  
C. Mixed alpha and beta: labetolol, dilutevlon, etc. |
| VI. Inhibition of catecholamine synthesis | A. Metyrosine |

Side Effects

The undesirable side effects of these sympatholytic agents are largely related to the pharmacological effects of the drugs, and agents with similar classification generally share side effects, though exceptions to the rule do occur and will be discussed in addition. In addition, certain agents are associated with special adverse effects that may be unrelated to their basic pharmacological actions.

The ganglionic blockers, while very effective in reducing blood pressure, especially in the standing or tilted position, have almost completely been supplanted by other antihypertensive agents. In addition to producing severe orthostatic hypotension with poor blood pressure control in the supine position, use of these drugs suffered from the effects of producing parasympathetic as well as sympathetic blockade. As a result, patients suffered from troublesome dry mouth, constipation, cycloplegia, urinary retention, and sexual dysfunction. Of these drugs, only trimethaphan, a drug of very rapid onset and short duration of action that is administered by intravenous infusion, is still sometimes used in controlling hypertensive crises or in controlled hypotension during surgery. Prolonged administration of this drug has been associated with reversible respiratory arrest, usually occurring only after more than 8 hours of continuous administration.6

Drugs that lower blood pressure through central adrenergic inhibition have in common the side effects of fatigue, sedation, and frequent incidence of depression at higher doses. Sedation is especially marked during the first several days of administration of drugs such as methyldopa, clonidine, and guanabenz, and in most patients, the sedative effect wanes after 3 or 4 days of administration. In those with a predisposition to depression, this serious psychiatric consequence is usually a contraindication to the continued use of these drugs. Reserpine, which has both central and peripheral antiadrenergic effects, may also produce prominent depression and sedative effects, but unlike the other agents, because of the slow accumulation of this drug in adrenergic tissues, the onsets of its therapeutic and side effects are delayed from 2 to 4 weeks after initiation of therapy at usual oral doses. Even in the absence of persistent sedation or depression, these centrally active drugs can also produce reduced mental acuity that is especially notable in patients who are intellectually very active, such as engineers, accountants, physicians, airline pilots, etc. These drugs also sensitize the patient to the effects of alcohol and other centrally active sedative drugs. In contrast to other sympatholytic drugs with central activity, the monoamine oxidase inhibitors are extremely potent and effective antidepressants and may produce excitement, euphoria, and even mania as undesirable behavioral side effects.

All of these drugs tend to produce greater falls of blood pressure in the standing position, and orthostatic or exercise-induced hypotension may limit the usable doses of these drugs. Prolonged use of these drugs as single agents tends to result in reduced antihypertensive effects due to sodium retention, and adjuvant diuretic therapy is often necessary.7 Adverse sexual effects, especially in men, may be manifest as a decrease in libido and/or decrease in potency and inability to achieve and maintain erection. The decrease in libido may be a more subtle manifestation of the sedation or depression produced by these agents. On the other hand, the effect on erectile potency is a much more complicated pharmacological effect dependent on complex peripheral mechanisms. Agents with some peripheral agonist activities, such as clonidine and guanabenz, may produce less of this peripheral sexual side effect. Dry mouth, nasal stuffiness, and diarrhea occur with larger doses of methyldopa and reserpine, and constipation is more common with clonidine and guanabenz. Methyldopa, by reducing central dopaminergic inhibition of prolactin release, also may pro-
duce gynecomastia in men and galactorrhea in both men and women.

Several of these drugs also have side effects that are specific to each of the agents. Up to 25% of patients taking 1 g of methyldopa daily for 6 months or more develop a positive direct Coombs' test. Only a small percentage of these patients then develop hemolytic anemia that is chronic and that tends to be partially compensated for by an increase in reticulocyte formation. In either event, the strongly positive Coombs' test can cause difficulty in performing accurate cross-matches for blood transfusion. Both the positive Coombs' test and the hemolysis wane over a period of weeks to months following discontinuation of the drug. The process can be accelerated by concomitant administration of glucocorticoids. A very small percentage of patients receiving methyldopa also develop an idiosyncratic allergic reaction manifested by fever, general malaise, and abnormalities of liver function that in the extreme can result in hepatic necrosis and death. This phenomenon appears to be partially dose related. The fever and abnormalities of liver functions can be titrated by increasing or decreasing methyldopa doses. Once the abnormalities have cleared, it is possible to test whether methyldopa was the offending agent by reinitiating the drug at a dose of 0.25 to 1.0 g and by following temperature and liver chemistries, which usually become abnormal again within 24 hours. However, it is not necessarily advisable to do so since a more serious liver reaction might occur, and it is probably preferable in the presence of fever associated with abnormalities of liver function to forego further use of this drug in favor of some other antihypertensive agent. Reserpine, uniquely among these agents, increases appetite, and its use may result in weight gain. In addition, when used chronically, reserpine increases gastric acid production and may exacerbate or produce gastritis and ulcer symptoms. Monoamine oxidase inhibitors are associated with the well-understood pressor responses to tyramine and other sympathomimetic agents that may be found in decongestants, cough preparations, appetite suppressants and diet aids, and in certain foods, most notably aged cheeses, pickled herring, liver, and red wines. All these substances may produce serious rises in blood pressure and hypertensive crises, even cerebral hemorrhage and myocardial infarction. The syndrome is readily reversed by the use of α-adrenergic blocking agents, preferably intravenous phentolamine, and the entire pressor response is usually limited to the duration of action of the food stuff or drug, rarely persisting beyond several hours. All possible offending substances are absolutely contraindicated in patients taking monoamine oxidase inhibitors, and patients should be specifically instructed and given a list of prohibited substances to avoid the possibility that they might have a serious adverse reaction. Abrupt discontinuation of clonidine and, to a lesser extent, methyldopa results in a withdrawal reaction characterized by excitation, sweating, exhilaration, tachycardia, insomnia, and rapid rise in blood pressure 18 to 36 hours later. Presor responses may be serious in patients taking large doses of these drugs, and the rise in pressure, while dramatic, rarely exceeds the pretreatment levels.

Those drugs that reduce blood pressure by inhibiting peripheral sympathetic neuronal discharge and activity are related to the prototype drug guanethidine. The major adverse effects associated with their use affect cardiovascular, gastrointestinal, and sexual function. All of these drugs produce bradycardia, and in very large doses, these drugs, as well as methyldopa and reserpine, decrease myocardial contractility and may produce severe congestive heart failure in patients with underlying impaired myocardial function. However, unlike the similar effects that may be seen with the use of β-blockers, these drugs are rarely used in the very large doses required to impair cardiac contractility since such large doses would produce other intolerable central nervous system, gastrointestinal, or orthostatic side effects. Fatigue, orthostatic hypotension, and especially exercise hypotension limit the use of larger doses of these drugs as does the development of severe diarrhea. Retrograde ejaculation is also a common complaint in males taking moderate to large doses. Guanethidine-like drugs also demonstrate an adverse interaction with tricyclic antidepressant drugs, which inhibit their uptake into the adrenergic nerve endings and reverse their antihypertensive effects. Because of its long duration of action, the effects of guanethidine decrease 7 to 10 days after discontinuation, while the effects of guanadrel last a day or less.

Metyrosine inhibits catecholamine synthesis, and while it may be effective in reducing blood pressure in some hypertensive patients, its use is usually reserved for the preoperative or chronic control of blood pressure in patients with pheochromocytoma. Since it is effective in both the central nervous system and the periphery, it shares many of the adverse side effects of the general sympatholytic agents. Most prominent are the central effects of sedation, fatigue, agitation, and, with larger doses, agitation and fine tremors may also develop, and in elderly patients especially, larger doses may produce Parkinson's syndrome because of central dopamine depletion. Though metyrosine is well absorbed from oral doses, it is quite insoluble in aqueous solutions. Patients who are dehydrated or who take doses in excess of 2 g daily may develop urinary crystalluria or even stones if there is inadequate urine formation. Metyrosine may produce severe watery diarrhea that appears to be an idiosyncratic mechanism since it may occur at low drug doses (less than 1 g daily) and that occurs in about 10 percent of patients taking larger doses independent of the degree of inhibition of norepinephrine synthesis. If it is imperative to continue the drug because of clinical circumstances related to the pheochromocytoma, it is usually possible to control the diarrhea by concomitant use of lomotil or related drugs. As with the effects of clonidine, guanabenz, and methyldopa, within 24 hours of the abrupt discontinuation of metyrosine, the patient experiences tem-
porary excitation, euphoria, insomnia, and a sustained rise in blood pressure until other therapy is instituted.

Sympatholytic drugs of all types are notably devoid of adverse chemical effects on serum electrolytes, lipids, glucose, and uric acid. Generally, symptomatic, rather than toxic, side effects limit drug use or dose. Thus, sympatholytic drugs are less likely to be effective and well tolerated when used alone, but by combined use with small doses of diuretics, the antihypertensive efficacy is augmented, and symptomatic side effects may be reduced or eliminated by lower drug doses.

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