

Evaluating Risk When Antihypertensive Medications Are Abruptly Discontinued in Research Subjects

by Mark C. Houston

Research protocols designed to study the efficacy and safety of new antihypertensive drugs commonly include abrupt discontinuation of antihypertensive therapy. This "washout" phase removes all previous medications from research subjects before the actual study begins. In addition, some patients in such studies may receive no effective therapy for quite a long time (placebo control). Other protocols study the effects of the abrupt withdrawal of the antihypertensive agent(s), in which case the goal may be to produce and evaluate the effects in their most severe form.

IRB members often question the safety of such protocols and the potential dangers such maneuvers present to patients. The risks of untreated hypertension, particularly if severe, even for short periods of time must be compared to benefits for the subject and to others. Numerous questions should be considered in such a decision, such as the severity of the patient's blood pressure before treatment was begun, concomitant cardiovascular diseases or other medical illness, and the type and dose of antihypertensive medication to be discontinued.

Few studies have been designed to evaluate the effects of abrupt discontinuation of antihypertensive drug treatment. Until recently confusion existed regarding the definition and classification of the discontinuation or withdrawal syndrome, its incidence, time of onset, physiologic and biochemical consequences, the individuals at risk, and the antihypertensive drugs most likely to be responsible.

There are several potential consequences of abrupt discontinuation of antihypertensive therapy.¹ In a very small percentage of patients, blood pressure remains normal in both the acute and chronic stages. A few patients experience signs and symptoms of sympathetic nervous system overactivity with a slight and slow rise in blood pressure. In a third group blood pressures gradually return without symptoms, to pretreatment levels over several weeks or months. Fourth, a greater number of patients experience a rapid asymptomatic return of blood

pressure to pretreatment levels within a few days. Finally, patients may experience "rebound" or "overshoot" hypertension. Rebound hypertension is a rapid (within 24-48 hours) return of blood pressure to pretreatment levels; it is associated with signs and symptoms of sympathetic nervous system overactivity (restlessness, anxiety, palpitations, abdominal pain, nausea and vomiting, insomnia, headaches, angina, tremor, sweating, tachycardia, etc.). Overshoot hypertension, on the other hand, is a rapid increase in blood pressure that exceeds any previous blood pressure measurement; it is also associated with sympathetic nervous system overactivity. Both rebound and overshoot hypertension are probably a consequence of the patient's natural tendency to become hypertensive off medications as well as some pharmacologic consequence of sudden withdrawal of certain antihypertensive medications.

Numerous antihypertensive drugs have been reported to cause a discontinuation syndrome (Table I), which may vary in severity from symptoms of excess sympathetic nervous system activity to rebound or overshoot hyper-

tension. Sometimes there are severe complications such as acute myocardial infarction, encephalopathy, preinfarction angina, cardiac arrhythmias, or sudden death. However, many early case reports and studies evaluated the discontinuation of three or four antihypertensive drugs at a time, making it difficult to interpret the effects of stopping a single drug. It appeared, however, that certain classes of drugs—particularly the beta-adrenoreceptor blocking agents and the central alpha agonist agents or combinations of these classes of antihypertensive medications—could intensify the syndrome if stopped suddenly. This is probably due to uninhibited alpha-receptor stimulation (constricts blood vessels and elevates blood pressure) and circulating catecholamines (hormones which elevate blood pressure) during beta blockade. Stopping one of the central alpha agonists abruptly and continuing the beta blocking agent such as propranolol can result in a similar problem. Diuretics may make signs and symptoms worse by depleting fluid volume, stimulating the sympathetic nervous system or possibly increasing the sensitivity of the catecholamine vaso-

TABLE I. Antihypertensive drugs reported to produce the discontinuation syndrome

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| (1) | Central alpha agonist agents |
| (A) | Clonidine |
| (B) | Alpha-methyldopa |
| (C) | Guanabenz |
| (2) | Beta-adrenoreceptor-blocking agents |
| (A) | Propranolol |
| (B) | Metoprolol |
| (C) | Oxprenolol |
| (D) | Other beta-blocking drugs |
| (3) | Other antihypertensive drugs |
| (A) | Guanethidine |
| (B) | Bethanidine |
| (C) | Reserpine |
| (D) | Diuretics |
| (E) | Saralasin |
| (4) | Combination drugs |
| (A) | Central acting drugs and beta-blockers |
| (B) | Central acting drugs and diuretics |
| (C) | Beta-blockers and diuretics |

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pressor response to discontinuing other drugs.^{1,2}

Accurate information regarding the syndrome after stopping individual antihypertensive agents must be obtained from prospective studies or well-documented case reports. The agents best studied include clonidine, methyl dopa, guanabenz, propranolol, metoprolol, and some other beta blockers. There have been isolated reports of the syndrome's occurrence upon discontinuing bethanidine, saralasin, captopril, diuretics, guanethidine, and reserpine. Few, if any, studies have evaluated vasodilating agents such as hydralazine, minoxidil, or prazosin because these agents are not used clinically except in combination with other drugs that enhance their effectiveness and mitigate their side effects.

Prospective studies where clonidine alone was discontinued showed an incidence of symptoms of sympathetic nervous system overactivity in 36% and overshoot hypertension in 1.7%. Signs and symptoms tended to occur within 24-48 hours after stopping clonidine. No patient developed overshoot hypertension if the discontinued dose was less than 1.2 mg/day. No major complications occurred and no deaths were reported in these patients. High levels of circulating and urinary catecholamines were noted in some patients. Re-institution of clonidine therapy resolved the hypertension and sympathetic overactivity.

Discontinuing methyl dopa abruptly may cause symptoms of sympathetic nervous system overactivity in 25% and overshoot hypertension in 4.4%. Signs and symptoms tended to occur within 24-72 hours in most patients but were not dose-related. Several of these patients developed major complications, including congestive heart failure or cerebrovascular accidents, and one patient died.

The effects of suddenly discontinuing beta-adrenergic blocking drugs, particularly propranolol and metoprolol have been well-studied. Stopping either of these agents and probably all beta blockers may result in overshoot hypertension in about 5%, symptoms of sympathetic nervous system overactivity in 43%, and major cardiovascular complications, including unstable angina (25%), acute myocardial infarction (10%), cardiac arrhythmias (2%), cerebrovascular accidents and sudden death (5%). These signs and symptoms may not occur for up to seven days with some beta blockers due to their prolonged effectiveness. Most problems, however, occur within the first 72

hours after discontinuation of these drugs. The syndrome may occur with virtually any dose of the beta blockers. Increased circulating levels of renin-angiotensin and catecholamines (both of these substances increase blood pressure) as well as an increased number and sensitivity of beta receptors is probably responsible.

Guanabenz may cause overshoot hypertension (4%) and symptoms of sympathetic overactivity (25-30%) within 24-48 hours after withdrawal. Signs and symptoms are probably dose-related and infrequent with doses of less than 32 mg/day. Reinstitution of guanabenz controlled symptoms and blood pressure. The mechanism of this discontinuation is probably similar to that for clonidine and methyl dopa.

Numerous mechanisms have been proposed for the discontinuation syndrome (Table II). Each class of antihypertensive agent probably has its own principal mechanism; however, numerous biochemical and physiologic changes contribute to the overall clinical signs and symptoms. Increased circulating levels of catecholamines, increased sensitivity of adrenergic receptors, and enhanced renin-angiotensin system activity are probably the major mechanisms by which central alpha agonists and beta blockers cause the syndrome.

The ability to predict which patients are most likely to develop problems after abruptly discontinuing antihypertensive agents depends on an understanding of predisposing factors (Table III). Certainly gradual tapering of these

agents is less likely to cause problems than abrupt cessation. Although central alpha agonists and beta blockers appear to have a higher incidence of clinical problems (they are better studied), apparently no class of antihypertensive agent is free of such problems. The combination of a central alpha agonist in conjunction with a beta blocker is best avoided if possible, particularly if volume contraction from diuretic use is present.

Patients with high pretreatment blood pressures who have good control, those with normal to high renin hypertension, renovascular hypertension, or renal disease are more likely to have discontinuation or withdrawal syndromes. Patients who are post-operative, have ischemic heart disease or other cardiovascular problems, or those taking excessively high doses of antihypertensive drugs are predisposed. Certainly, patients may develop complications such as stroke, acute myocardial infarction, congestive heart failure, or numerous other problems as a result of absence of therapy chronically, but not necessarily, as a direct result of discontinuation of therapy acutely (i.e., no cause-effect relationship).

Prevention and recognition of the discontinuation syndrome is important to any physician engaged in clinical investigation of hypertension in human subjects. The signs and symptoms have been well-described and are easy to recognize. Appearance of clinical events usually occurs within 24-48 hours after stopping the drugs but may

TABLE II. Postulated mechanisms of the discontinuation syndrome

- (1) Central-acting drugs
 - (A) Breakthrough of autoregulation of cerebral blood flow
 - (B) Increased levels of circulating catecholamines (norepinephrine)
 - (C) Increased sensitivity of adrenergic receptors to norepinephrine
 - (D) Enhanced renin-angiotensin system activity
 - (E) Reduced vagal function
- (2) Beta-adrenoreceptor drugs
 - (A) Increased myocardial oxygen requirements
 - (B) Alteration of oxyhemoglobin-dissociation curve
 - (C) Increased platelet adhesiveness and aggregation
 - (D) Asymptomatic progression of coronary artery disease during treatment
 - (E) Increased renin-angiotensin system activity
 - (F) Increased levels of circulating thyroid hormones
 - (G) Increased sensitivity of receptors of catecholamines
 - (H) Increased levels of circulating catecholamines

be delayed for up to seven days in drugs with prolonged effectiveness (some beta blockers). Gradual tapering of the antihypertensive drugs over ten days will usually avoid clinical problems. If problems should occur, re-institution of the previously administered drug will alleviate symptoms and control blood pressure.

Study protocols that are designed to study new antihypertensive agents after a "washout" period should slowly reduce the dose of the previously used antihypertensive drugs by one-tenth of the dose each day over the ten-day period to avoid withdrawal symptoms or complications. This will usually avoid any adverse cardiovascular effects due to a direct cause-effect relationship of having stopped the drug abruptly because of the lack of increased numbers of hypersensitive receptors or high circulating blood hormone levels that would elevate blood pressure. On the other hand, protocols designed to study the effects of abruptly discontinuing antihypertensive agents require more intensive monitoring of blood pressure, pulse, and cardiac status with continuous electrocardiographic monitors; there should also be frequent monitoring of the overall clinical condition of the patient, looking particularly for chest pain, shortness of breath, headache, and other signs and symptoms mentioned previously. Both groups of patients should be under close supervision to monitor potential complications (preferably in a hospital); the latter group should be in an intensive care setting. Such research strategies will reduce risk without harming design.

The frequency of various complications of abrupt withdrawal of antihypertensive therapy is difficult to determine precisely from published studies. However, based upon this review of prospective studies and case reports in which single antihypertensive agents were stopped permits the development of some general guidelines regarding rebound and overshoot hypertension and other morbid cardiovascular events in such patients.

Abrupt discontinuation of antihypertensive medications certainly creates a greater risk of serious complications than does *gradual* withdrawal of the drugs. All risks should be explained to the patients. Those at high risk—patients over age 50, those with known cardiovascular disease (angina, previous myocardial infarction, congestive heart failure, etc.) or other severe medical illness (lung disease, kidney failure, etc.) and those who had severe hypertension (diastolic blood pressure over

TABLE III. Predisposing factors for the discontinuation syndrome

- (1) Abrupt discontinuation of antihypertensive drug therapy
- (2) Central alpha agonists or beta blockers
- (3) Combination drug therapy—especially central alpha agonists with beta blockers, diuretics
- (4) Level of pretreatment blood pressure
- (5) Adequacy of blood pressure control on therapy
- (6) Renin status—high or normal renin hypertension
- (7) Renovascular hypertension or renal disease
- (8) Postoperative state
- (9) Ischemic heart disease
- (10) High daily doses of antihypertensive drug

120 mm Hg) prior to institution of antihypertensive therapy—should be excluded from such research protocols. The risk is low for a younger patient in otherwise good health who has only mild to moderate hypertension; such patients make the best candidates for such studies.

Some subjects may have serious complications—e.g., myocardial infarction—during periods of withdrawal of antihypertensive medication. Often it is extremely difficult to distinguish those complications due to drug withdrawal from those the patients would have sustained in the natural course of their treated disease.

Awareness of the potential complications of antihypertensive medication withdrawal, recognition of the high-risk patient, and understanding how to prevent and treat such problems, coupled with careful patient monitoring, should minimize risk to patients in these studies.

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