

Maximum Antihypertensive Effect From Different Classes of Antihypertensives

QUESTION

How long does it take to get the maximum antihypertensive effect from different classes of antihypertensives?

ANSWER

SEARCH STRATEGY

Using MEDLINE, the keywords “hypertension,” “drug therapy,” and “pharmacodynamic” identified English-language and review articles since 1990. Additional pertinent primary articles were then identified from the review article reference lists. The difficulty in determining the answer to this question was a lack of published randomized clinical trials and limited manufacturer data that focus on the blood pressure response for a fixed interval of time. Since blood pressure response is commonly reported at 4 to 8 weeks in clinical studies, the data for answering this question were primarily obtained from manufacturers' package inserts. The American Hospital Formulary Service was used to reinforce data.

BACKGROUND

In asymptomatic patients with uncomplicated (stage 1 or 2) hypertension, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI)¹ has guided clinicians to adjust medication therapy after 1 to 2 months if blood pressure remains uncontrolled. This general guideline is helpful in managing outpatients; however, knowing the time to maximal antihypertensive effect may help us with outpatient drug titration in 2 ways. First, drug therapy adjustments may be made sooner. Second, overaggressive blood pressure reduction by adding multiple antihypertensive medications when the original therapy has not yet reached its peak effect could be avoided.

The activity of antihypertensive therapies involves specific pharmacokinetic and pharmacodynamic actions of the agent used. If the agent has a long elimination half-life, it may take several days to achieve the steady-state plasma level. Long half-lives also provide a gradual

pharmacodynamic onset of action, which is often preferred. Rapid reduction of blood pressure can precipitate renal, cerebral, or coronary ischemia. Avoiding these complications while minimizing adverse effects typically calls for low doses of antihypertensive medication as the initial blood pressure management. Blood pressure titration is then based on the patient's symptoms, the blood pressure goal, and the drug therapy being used. For outpatient therapy, the current guidelines recommend long-acting once-daily agents, if available.¹

The current guidelines provide specific drug therapy recommendations for patients with “compelling indications” and “comorbid conditions.” If there is no indication for another type of medication, a diuretic or β -blocker is recommended by JNC-VI. The major classes of oral therapies in the outpatient arena are described below.

THIAZIDE DIURETICS

The thiazide diuretic hydrochlorothiazide can be used as initial therapy or in combination. The JNC-VI guideline recommends that thiazides be considered in patients who do not respond adequately to an agent from a different class. The precise antihypertensive mechanism of thiazides has not been determined. The onset of hypotensive effect is within the first week, and the hypotensive action dissipates during the first week following discontinuation.^{2,3} It is generally accepted that the dose of thiazide diuretics can be adjusted after 4 to 8 weeks.² Most patients (50%-60%) respond to thiazide diuretics. The dose of 12.5 mg of hydrochlorothiazide reduces blood pressure in approximately one half to two thirds of potential responders. Additional dosage titration to 25 mg increases the response rate by an additional 10% to 15%. Further dosage titration provides minimal blood pressure reduction at the expense of additional adverse effects.⁴

α -BLOCKERS

The use of the α -blockers terazosin and doxazosin should begin with low doses to prevent postural hypotension. The dosage of α -blockers should be adjusted no more frequently than every 2 weeks with close monitoring of upright blood pressure measurement and symptomatic orthostasis. The available titration starter pack of doxazosin contains a 2-week supply of 1-mg tablets, followed by a 2-week supply of 2-mg tablets and, finally, 4-mg tablets.

Additional dosage doubling with doxazosin can be performed at 2-week intervals to a maximal dose of 16 mg.^{5,6}

The starter pack of terazosin differs from the above description in that it provides a 3-day supply of 1-mg tablets followed by a 2-week supply of 2-mg tablets and then 5-mg tablets. Dosage titration beyond the 5-mg dose can be made every 2 weeks to a maximum dose of 20 mg.^{7,8}

β-BLOCKERS

In dosages of 150 to 450 mg/d, the β-blocker metoprolol causes systolic blood pressure reductions of 20 mm Hg within 1 week in healthy patients.^{9,10} The initial dose of atenolol is 50 mg or 25 mg for elderly patients. The full antihypertensive effect of atenolol at the initial dosage is seen in 1 to 2 weeks. The maximal antihypertensive dose of atenolol is 100 mg; higher doses seem to provide no additional benefit.^{11,12}

α-β-BLOCKERS

The use of oral labetalol to lower blood pressure has demonstrated that the onset of action occurs at 20 minutes and the maximum steady-state blood pressure response, with twice-daily dosing, occurs within 1 to 3 days. The initial dosage of 100 mg twice daily can be titrated every 2 or 3 days. The adverse effects of nausea and dizziness may be minimized or avoided if dosage titration occurs at 2- to 4-week intervals.¹³

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

The hypotensive action of inhibiting the angiotensin-converting enzyme can be abrupt. Single oral doses of enalapril may reduce the diastolic and systolic blood pressure by 15% to 20% after 6 to 8 hours. As the dose is increased past 10 mg, the duration of blood pressure response tends to extend, thereby allowing once-daily dosing. The initial oral dose of enalapril is usually 2.5 to 5 mg daily for hypertension and the usual dosage range is 5 to 40 mg once daily.^{14,15} The dosage may be doubled every 1 to 4 weeks to achieve the desired response.^{15,16} Similarly, the dose of ramipril is recommended to be adjusted from the initial dose of 1.25 to 2.5 mg once daily to a usual maintenance dose of 2.5 to 20 mg with adjustments made no more frequently than 2-week intervals.¹⁷ Additionally, the initiation of trandolapril is recommended to be 1 or 2 mg and adjusted no more often than weekly. The usual maintenance dose of trandolapril is 2 to 4 mg.^{18,19}

ANGIOTENSIN II RECEPTOR BLOCKERS

Angiotensin receptor blockers effectively lower blood pressure. Losartan demonstrates antihypertensive effects

within 1 week. In some studies, the maximal effect occurred in 3 to 6 weeks.²⁰ The recommended initial dose of valsartan is 80 mg daily. Valsartan has a substantial effect on blood pressure within 2 weeks, with maximal reduction generally attained after 4 weeks. In patients who do not achieve the desired response, it may be advisable to add a diuretic before increasing the dose of valsartan.^{21,22}

CALCIUM CHANNEL BLOCKERS

Historically, short-acting calcium channel blockers have been used to rapidly reduce blood pressure in patients with hypertensive crisis. The use of short-acting nifedipine for this purpose is no longer recommended owing to safety concerns.¹ However, this use demonstrated nifedipine's rapid onset of action. The long-acting formulations can be expected to provide blood pressure reductions that can be titrated every 1 to 2 weeks.^{23,24} Extended-release verapamil demonstrates antihypertensive effects with the first week of therapy and the titration can be performed on a weekly basis.^{25,26} The continuous delivery system for diltiazem usually provides maximal antihypertensive effect after 2 weeks of therapy.^{27,28}

CENTRALLY ACTING α-AGONISTS

The onset of blood pressure reduction is seen within 30 to 60 minutes after an oral dose of clonidine. Antihypertensive effects last up to 8 to 12 hours. This short duration requires clonidine to be administered 2 or 3 times a day for long-term therapy.^{29,30} The availability of the clonidine patch provides continuous delivery in a weekly delivery system. Because of slow subcutaneous absorption from the patch, the therapeutic plasma concentrations are not achieved for 2 to 3 days following initiation. The patch dosage can be adjusted after 1 to 2 weeks.^{30,31}

As a general rule, any single agent is effective in only about 50% to 60% of patients with mild to moderate essential hypertension when average doses are used, and even with higher doses the response rates may only reach 70%.³² Because higher doses lead to more adverse effects, combination therapy with lower doses of medications with different mechanisms of action may be considered.¹ One problem with hypertensive medication titration is that abrupt blood pressure reduction may cause fatigue. Slow titration, as advised by the JNC-VI guidelines, will help minimize this complaint, and allow patients to gently adjust to a lower blood pressure.

BOTTOM LINE

Data exist for adjusting doses of various α-blockers, β-blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, and clonidine at intervals of 2 weeks

or less. However, antihypertensive medication titration at intervals of 1 to 2 months seems to be appropriate for all commonly used drug classes. Additionally, gradual titration of medication may improve tolerability.

Peter G. Koval, PharmD
Eve M. Kochis, PharmD
1125 N Church St
Greensboro, NC 27401
(e-mail: peter.koval@mosescscone.com)

REFERENCES

1. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *National High Blood Pressure Education Program: The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*. Bethesda, Md: Public Health Service, National Institutes of Health, National Heart Lung and Blood Institute; 1997. NIH publication 98-4080.
2. American Hospital Formulary Service. Thiazide general statement. In: *AHFS Drug Information 1999*. Bethesda, Md: American Society of Hospital Pharmacists; 1999:2297-2301.
3. Hydrodiuril [package insert]. Whitehouse Station, NJ: Merck & Co Inc; 1986.
4. Moser M. *Clinical Management of Hypertension*. 2nd ed. Caddo, Okla: Professional Communications Inc; 1997.
5. American Hospital Formulary Service. *AHFS Drug Information 1999*. Bethesda, Md: American Society of Hospital Pharmacists; 1999:1633-1636. Terazosin hydrochloride monograph.
6. Cardura [package insert]. New York, NY: Pfizer Inc; 1997.
7. American Hospital Formulary Service. Doxazosin mesylate monograph. In: *AHFS Drug Information 1999*. Bethesda, Md: American Society of Hospital Pharmacists; 1999:1581-1584.
8. Hytrin [package insert]. North Chicago, Ill: Abbott Laboratories Inc; 1996.
9. American Hospital Formulary Service. *AHFS Drug Information 1999*. Bethesda, Md: American Society of Hospital Pharmacists; 1999:1461-1467. Metoprolol monograph.
10. Toprol XL [package insert]. Westboro, Mass: Astra Pharmaceuticals Inc; 1998.
11. American Hospital Formulary Service. *AHFS Drug Information 1999*. Bethesda, Md: American Society of Hospital Pharmacists; 1999:1388-1392. Atenolol monograph.
12. Tenormin [package insert]. Wilmington, Del: Zeneca Pharmaceuticals; 1997.
13. American Hospital Formulary Service. *AHFS Drug Information 1999*. Bethesda, Md: American Society of Hospital Pharmacists; 1999:1602-1609. Labetolol hydrochloride monograph.
14. Vasotec [package insert]. Whitehouse Station, NJ: Merck & Co Inc; 1997.
15. American Hospital Formulary Service. *AHFS Drug Information 1999*. Bethesda, Md: American Society of Hospital Pharmacists; 1999:1420-1431. Enalapril/enalapril maleate monograph.
16. Todd PA, Goa KL. Enalapril: a reappraisal of its pharmacology and therapeutic use in hypertension. *Drugs*. 1992;43:346-81.
17. American Hospital Formulary Service. *AHFS Drug Information 1999*. Bethesda, Md: American Society of Hospital Pharmacists; 1999:1509-1510. Ramipril monograph.
18. Mavik [package insert]. Whippany, NJ: Knoll Pharmaceuticals; 1997.
19. American Hospital Formulary Service. *AHFS Drug Information 1999*. Bethesda, Md: American Society of Hospital Pharmacists; 1999:1637-1638. Trandolapril monograph.
20. Cozaar [package insert]. Whitehouse Station, NJ: Merck and Co Inc; 1998.
21. American Hospital Formulary Service. *AHFS Drug Information 1999*. Bethesda, Md: American Society of Hospital Pharmacists; 1999:1638-1639. Valsartan monograph.
22. Diovan [package insert]. Princeton, NJ: Novartis Pharmaceuticals; 1997.
23. American Hospital Formulary Service. *AHFS Drug Information 1999*. Bethesda, Md: American Society of Hospital Pharmacists; 1999:1474-1480. Nifedipine monograph.
24. Procardia XL [package insert]. New York, NY: Pfizer Inc; 1997.
25. American Hospital Formulary Service. *AHFS Drug Information 1999*. Bethesda, Md: American Society of Hospital Pharmacists; 1999:1522-1531. Verapamil monograph.
26. Isoptin SR [package insert]. Whippany, NJ: Knoll Pharmaceuticals; 1996.
27. American Hospital Formulary Service. *AHFS Drug Information 1999*. Bethesda, Md: American Society of Hospital Pharmacists; 1999:1408-1416. Diltiazem monograph.
28. Cardizem CD [package insert]. Sommerville, NJ: Hoechst-Roussel Pharmaceuticals Inc; 1995.
29. Catapres [package insert]. Ridgefield, Conn: Boehringer Ingelheim Pharmaceuticals Inc; 1996.
30. American Hospital Formulary Service. *AHFS Drug Information 1999*. Bethesda, Md: American Society of Hospital Pharmacists; 1999:1572-1577. Clonidine monograph.
31. Catapres-TTS [package insert]. Ridgefield, Conn: Boehringer Ingelheim Pharmaceuticals Inc; 1996.
32. Opie LH. Choosing the correct drug for the individual hypertensive patient. *Drugs*. 1992;44(suppl 1):147-155.

Clinical Pearl

The Fear of Hip Fracture

Among 194 women aged 75 or older surveyed in England, 80% would rather be dead than experience a bad hip fracture that resulted in admission to a nursing home. (*BMJ*. 2000;329:341-346).