Our Own Worst Enemy: Pharmacologic Mechanisms of Hypertension

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Drug-induced hypertension is often an unrecognized cause of resistant or secondary hypertension. It is defined as hypertension resulting from the unintended effect of a drug or from a drug's antagonistic effect on antihypertensive medications. The main mechanisms of drug-induced hypertension, when categorized broadly, include volume retention and sympathomimetic effects. These mechanisms along with management strategies will be further discussed in this article.

Key Words: Drug induced, Hypertension, Secondary hypertension, Resistant hypertension, Blood pressure

INTRODUCTION

Drug-induced hypertension is often an unrecognized cause of secondary or resistant hypertension. It is defined as hypertension resulting from the unintended effect of a drug or from a drug's antagonistic effect on antihypertensive medications. The exact incidence is unknown, but considering the high prevalence of polypharmacy, it is reasonable to assume that many patients with hypertension are taking a drug expected to exacerbate their condition. The US Food and Drug Administration (FDA) has no uniformly agreed upon definition or method for identifying clinically significant drug-induced hypertension during the new drug approval process.[1] The mean change in blood pressure in millimeters of mercury for the test drug is compared with placebo, and if the data are statistically significant, the FDA acknowledges that a larger study would be necessary to determine the causality of increased cardiovascular or thrombotic events. Some recent examples of drugs that have been removed from the market because of adverse cardiovascular effects include rofecoxib (Vioxx), valdecoxib (Bextra), and sibutramine (Meridia), all of which also increased blood pressure.[2] This emphasizes the importance of better understanding the sequelae of drug-induced hypertension.

The individual hypertensive response to a particular agent can vary widely between individuals, from no effect to a severe increase.[3] However, even in those experiencing small changes in blood pressure, epidemiologic data demonstrate that there is a continuous relationship between blood pressure elevations and adverse cardiovascular outcomes. At ages 40 to 69 years, a 2 mm Hg decrease in systolic blood pressure (SBP) reduces the risk of stroke mortality by 10% and vascular or ischemic heart disease mortality by 7%.[4] Therefore, drug-induced hypertension may have a significant impact in morbidity and mortality.

The main mechanisms of drug-induced hypertension, when categorized broadly, include volume retention and sympathomimetic effects. These mechanisms along with management strategies will be further discussed in this article. Specific management strategies appear in Table 1.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND CYCLOOXYGENASE-2 INHIBITORS

The prevalence of non-steroidal anti-inflammatory drug (NSAID) use makes this drug class one of the most frequent causes of drug-induced hypertension.[3] The mean arterial blood pressure increase is typically around 5 mm Hg but is more pronounced in patients with hypertension and impaired blood flow to the kidney (eg, the elderly or CKD) or those with congestive heart failure.[5,6] NSAIDs and cyclooxygenase-2 inhibitors reduce prostaglandins, especially E_2 and I_2, which possess a vasodilatory and natriuretic effect. This reduction in natriuresis and kidney arterial blood flow increases sodium and water retention and activates the renin-angiotensin-aldosterone system (RAAS).[5] NSAIDs not only increase blood pressure but also attenuate the response of antihypertensive medications that use these mechanisms, specifically angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), direct renin inhibitors, beta-blockers, and diuretics. The efficacy of calcium channel blockers and centrally acting drugs (eg, clonidine) are not affected by NSAIDs and cyclooxygenase-2 inhibitors, making these good therapeutic options if NSAIDs cannot be stopped or dose reduced.[5] The use of acetaminophen as a replacement for an NSAID can be considered, but acetaminophen does not have anti-inflammatory properties, which may diminish the ability to alleviate pain.

CORTICOSTEROIDS AND LICORICE

At least 20% of patients using synthetic corticosteroids have hypertension.[7] Cortisol at doses of 80 to 200 mg/d can increase SBP by 15 mm Hg within 24 hours[8] and peaks at day 4 or 5.[9] The classic explanation of this blood pressure elevation is stimulation by cortisol of the mineralocorticoid receptor resulting in kidney sodium retention and increased volume. The corticosteroids with the

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highest mineralocorticoid activity, such as cortisone and hydrocortisone, cause the greatest amount of fluid retention.[3] Treatment with spironolactone to antagonize the mineralocorticoid receptor does not necessarily treat corticosteroid-induced hypertension,[10,11] alluding to other proposed mechanisms, including increased activation of angiotensin II,[5] increased sympathetic activity,[5] alteration in nitric oxide (NO) activity,[1,12] and an unclear role of glucocorticoid receptors.[13] Treatment of corticosteroid-induced hypertension includes cessation or reduction of steroid therapy and dietary sodium restriction. Diuretics can be used to reduce volume overload.[5] Because long-term corticosteroid use predisposes patients to osteoporosis, thiazide diuretics are preferred over loop diuretics to reduce calcium excretion.[15] Adding ARBs or ACEIs may help counteract the proposed effects of angiotensin II.[5,8,12] Similarly to corticosteroids, licorice root (*Glycyrrhiza glabra*) can cause excess cortisol. It is often used as a flavorant in smokeless tobacco and as an herbal product for the treatment of gastritis, stomach ulcers, and constipation. It inhibits 11β-hydroxysteroid dehydrogenase type 2 from inactivating cortisol resulting in sodium reabsorption and potassium excretion leading to a phenotype similar to an acquired state of apparent mineralocorticoid excess syndrome.[14] It is commonly associated with hypokalemia and often seen in association with a high salt intake. This product should be avoided in patients with hypertension.

CLINICAL SUMMARY

- The main mechanisms of drug-induced hypertension are volume retention and sympathomimetic effects.
- Discontinuation of the offending agent or a dose reduction can often reverse or improve drug-induced hypertension.
- If drug discontinuation is not possible, use medications that counteract the underlying mechanism of the drug-induced hypertension (eg, a dihydropyridine calcium channel blocker for agents that cause peripheral vasoconstriction or a diuretic for agents that cause sodium and fluid retention.)

ERYTHROPOIESIS-STIMULATING AGENTS

Erythropoiesis-stimulating agents (ESAs), used for the treatment of anemia in CKD or cancer, can cause or worsen hypertension in 20% to 30% of patients with an onset anywhere from 2 weeks to 4 months after starting treatment.[16] An observational study ($n = 41$) identified an increased mean blood pressure of ≥5 mm Hg 30 minutes after 1 dose of erythropoietin in 44% of hemodialysis and 31% of chronic kidney failure patients.[86] Hypertensive encephalopathy and seizure have been reported in patients with CKD.[19,20] Typically, ESA-induced hypertension is associated with higher mean doses and possibly a higher target hemoglobin level. These agents were originally thought to increase blood pressure because of increased blood viscosity and red blood cell mass, but vasoconstricting mechanisms appear to play an important role, including increases in endothelin-1 and thromboxane and decreases in prostacyclin,[1] a rise in cytosolic calcium in smooth muscle cells,[17] and vascular hypertrophy.[18] Uncontrolled hypertension is a contraindication for use and should be controlled before starting ESAs. Management options include dose reduction to a target hemoglobin level no greater than 11 g/dL, cessation of therapy, antihypertensive agents of any class, preference for subcutaneous over intravenous administration, and optimization of volume status by dialysis (if applicable).[8,19,20]

CALCINEURIN INHIBITORS

Cyclosporine and tacrolimus, immunosuppresants via T-cell modulation, result in hypertension in 8% to 53% of individuals.[21] The average increase in mean arterial blood pressure is 5 to 11 mm Hg and is dose dependent.[22] They exert their hypertensive effects from vasoconstriction and increased kidney sodium retention[23,24] and activation of the kidney sodium chloride cotransporter.[89] The vasoconstriction is likely because of endothelin production and decreased NO, as opposed to an increase in angiotensin.[23,25] Thus, ACEI and ARB therapy has not been found to be advantageous and can actually be deleterious because of additive hyperkalemia and kidney dysfunction when combined with the calcineurin inhibitors. Similarly, the use of aldosterone blockers would necessitate close monitoring of potassium and kidney function if given with calcineurin inhibitors.

In managing this condition, switching from cyclosporine to tacrolimus can be considered because the effects on the vasculature are less pronounced with tacrolimus.[26,27] Withdrawal of the calcineurin inhibitor and limiting the dose will decrease blood pressure, but this is often not an option to prevent organ transplant rejection. Calcium channel blockers are the drug class of choice to limit the vasoconstrictive properties of calcineurin inhibitors. The dihydropyridine calcium channel blockers (DCCBs; eg, amlodipine) are preferred for their peripheral vasodilatory effects and the reduced likelihood of increasing serum concentrations of tacrolimus or cyclosporine drug levels via cytochrome P450 3A4 inhibition.[28] Additionally, thiazide diuretics, which block kidney sodium chloride cotransport, may have a role in reversing tacrolimus-induced hypertension.[89]

ANTIDEPRESSANTS AND ANTIPSYCHOTICS

Patients receiving bupropion, a dopamine-reuptake inhibitor, demonstrated significant elevations in supine blood pressure and were more likely to experience an orthostatic drop in blood pressure.[29] Minor changes in pulse and blood pressure were reported in smoking cessation trials[30]; however, the risk of hypertension was greatest in patients treated with concomitant transdermal nicotine therapy.[31] In a small depression trial, approximately 5% of patients with stable heart failure required bupropion discontinuation because of hypertension.[31]

Blood pressure elevations from the monoamine oxidase inhibitors (MAOIs) are typically associated with ingestion of tyramine-rich foods,[5,32] which is why a strict tyramine avoidance diet should be implemented.