CME Topic

Secondary Hypertension due to Drugs and Toxins

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Abstract: This review summarizes the current state of knowledge about drugs, other chemical substances, and toxins on blood pressure. Many classes of drugs, such as steroids, sympathomimetic amines, immunosuppressive agents, nonsteroidal anti-inflammatory agents, antidepressants, erythropoietin, substances of abuse and other agents can induce transient or sustained hypertension, exacerbate well-controlled hypertension, antagonize the effects of antihypertensive therapy, or precipitate hypertensive emergencies. Heightened awareness on the part of the physician is important to avoid unnecessary tests in search for other etiologies, and to reduce antihypertensive medication prescriptions by eliminating contributing agents whenever possible. These agents represent an important modifiable cause of secondary or resistant hypertension.

Key Words: hypertension, toxins, secondary, resistant, drugs

Drugs, herbal preparations and environmental toxins are important and modifiable causes of hypertension. The presence of other drugs or chemicals which elevate blood pressure directly or through secondary phenomena (drug interactions, renal impairment) can produce resistant hypertension (blood pressure remaining above goal despite treatment with three or more antihypertensive medications at or near maximal doses), increase antihypertensive drug requirements, or cause loss of blood pressure control in previously controlled hypertensives. A thorough history, addressing present and past medication use, over-the-counter and "natural" supplements, as well as environmental exposures, should be part of every evaluation of patients with marked, refractory, or atypical (by age and risk profile) hypertension, before performance of expensive or invasive tests for other etiologies.

Steroids

Corticosteroids

Although hypertension develops in 70 to 80% of patients with Cushing syndrome, it is seen in only 15 to 20% of patients treated with high-dose synthetic corticosteroids, which have less mineralocorticoid activity than cortisol.[1,2] In healthy subjects, a several day infusion of cortisol or oral ingestion of dexamethasone leads to increased systolic and diastolic blood pressure parallel with increased arterial resistance.[3–5] Patients receiving therapeutic glucocorticoids also have a greater sensitivity to catecholamines from a direct effect of the drugs on vascular tissue.[5] Natural licorice and its derivative carbenoxonole cause a syndrome of apparent mineralocorticoid excess, with hypertension, hypokalemic metabolic alkalosis, and suppression of the renin-angiotensin-aldosterone system.[6] The mechanism is inhibition of 11 β-hydroxysteroid dehydrogenase (11 β–HSD),[7] preventing the deactivation of cortisol to cortisone, permitting circulating endogenous glucocorticoids to bind to mineralocorticoid (and possibly glucocorticoid) receptors, and inducing a mineralocorticoid-like response.[8] Fluoroprednisolone and 9α–fluorocortisol have considerable direct mineralocorticoid activity; in large amounts they produce arterial hypertension with a clinical picture of pseudohyperaldosteronism (increased exchangeable sodium and blood volume, hypokalemic metabolic alkalosis, and suppressed plasma renin and

Key Points

- Certain drugs, herbal preparations and environmental toxins are important and modifiable causes of hypertension, sometimes contributing to hypertensive emergencies.
- These agents can induce transient or sustained hypertension, exacerbate well-controlled hypertension, or antagonize the effects of antihypertensive therapy.
- Heightened awareness on the part of the treating physician is important to avoid unnecessary and expensive testing.

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aldosterone levels).[9] Prolonged use of high-dose ketoconazole and other drugs that inhibit endogenous steroid catabolism can lead to mineralocorticoid-related hypertension.[10] Discontinuation of interacting drugs and/or steroids is recommended to ameliorate steroid-induced hypertension. When steroid therapy is unavoidable, the resultant hypertension usually responds to fluid restriction and diuretics.[11]

Sex Hormones

Hypertension is 2 to 3 times more common in women taking oral contraceptives than in control patients.[12] It is especially common among individuals with a history of elevated blood pressure during pregnancy, those with a family history of hypertension, smokers, blacks, obese women, and diabetics.[13] High-dose estrogens may induce sodium retention and volume expansion through an interaction with mineralocorticoid receptors or effects on 11 β-HSD activity.[14] Sex hormones also increase plasma concentrations of angiotensinogen.[15] Danazol, a semisynthetic androgen used to treat endometriosis and hereditary angioedema (and abused as a performance-enhancing androgen by athletes) can induce hypertension through salt and water retention; blood pressure usually responds to low-dose diuretics if the drug cannot be stopped.[16]

Immunosuppressive Agents

Cyclosporine

Hypertension is reported in as many as 50 to 70% of patients undergoing renal, hepatic or heart transplants treated with cyclosporine. This drug can cause new onset, or exacerbation of pre-existing, hypertension. Most studies have shown no association with race or gender. Typically, patients develop mild to moderate hypertension, with severe hypertension occurring infrequently.[17] Enhanced renal vasoconstriction with decreased excretion of salt and water produces volume-dependent (low renin) hypertension.[18] Blood pressure may be difficult to control when cyclosporine is continued, and although this typically decreases after drug discontinuation, it may not resolve completely.[19] Although diuretics are effective treatment, they may exacerbate prerenal azotemia. Calcium channel antagonists are the most consistently effective agents, but can increase cyclosporine blood levels through cytochrome P450-mediated metabolism of cyclosporine.[20]

Recombinant Human Erythropoietin

Recombinant human erythropoietin (rHuEPO) has dramatically improved the care of patients with renal failure, but can increase blood pressure in a dose-dependent fashion and cause hypertension in 20 to 33% of recipients.[21] A family history and a prior personal history of hypertension increase this risk.[22,23] Hypertension may develop 2 to 16 weeks after starting rHuEPO,[22] does not correlate with an increase in red cell mass, and can occur even with no change in hematocrit.[24] Chronic exogenous EPO results in a reduction of nitric oxide-mediated vasodilation via elevated resting cytosolic calcium concentrations, and directly constricts resistance arterioles.[25] Initially, this effect is countered by acute elevations of nitric oxide and cGMP. When taken chronically however, EPO promotes vascular smooth muscle cell growth, vascular remodeling and medial hypertrophy, maintaining blood pressure elevation.[25,26] Hypertension from rHuEPO is generally easily controlled; in one report, 42% of patients were effectively treated with a single agent.[27] In the chronic hemodialysis population, hypertension can also be treated with fluid removal and conventional antihypertensive therapy; when unsuccessful, the rHuEPO dose should be lowered, or therapy held for several weeks. When refractory to these approaches, phlebotomy (500 mL) can also help.[28]

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the medications most commonly prescribed to treat pain and inflammation, but hypertension, renal and gastrointestinal toxicity can limit tolerance. NSAIDs cause sodium retention, enhance the vasoconstrictor response to pressor hormones, and antagonize the effects of antihypertensive drugs.[29] Hypertension is caused by cyclooxygenase inhibition, which reduces vasodilatory prostaglandin synthesis. These prostaglandins promote natriuresis and modulate systemic and renal vasodilation, glomerular filtration, and sympathetic nerve transmission. The net effects of NSAIDs are salt and water retention, loss of renal vasodilation, and increased sympathetic activity with resultant suppression of renin activity.[30] Two meta-analyses confirmed that NSAIDs increase mean arterial pressure an average of 4 to 5 mm Hg.[31,32] They can antagonize the actions of most antihypertensive agents, except calcium channel blockers and perhaps central sympatholytics, whose effects are largely unrelated to prostaglandin actions.[33] Ibuprofen, piroxicam and naproxen demonstrate the greatest blood pressure effects, whereas sulindac and full-dose aspirin exhibit the least effects.[30,34] Low-dose aspirin has no effect on blood pressure in hypertensive patients, but selective cyclooxygenase-2 inhibitors (rofecoxib and celecoxib) increase pressure in a dose-dependent manner.[35] Both the incidence and severity of hypertension are greater with rofecoxib than with celecoxib or naproxen.[36] Since NSAIDs are available over the counter, clinicians must consider their contribution to new onset and refractory hypertension.

Therapeutic Sympathomimetic Amines

Sympathomimetic amines produce α-adrenergic agonism by postsynaptic receptor binding, facilitated norepinephrine release from neuronal storage sites, or both mechanisms.[37] Over-the-counter nasal sprays, oral decongestants, and many appetite suppressants contain the vasoconstrictors ephedrine,

pseudoephedrine and oxymetazoline. They can both cause and counteract the pharmacological treatment of hypertension.[37–40] Hypertension has occurred with ocular administration of dipivefrin (epinephrine) used to treat simple glaucoma, and ocular phenylephrine.[41] Premature neonates, the elderly, and those with idiopathic orthostatic hypotension are at greater risk from the latter drug.[42]

Patients frequently forget to include over-the-counter products in their medication history, and their ubiquitous nature makes legal sympathomimetic amines frequent contributors to hypertension. Discontinuing the offending agent will usually normalize blood pressure but when continuation is necessary, antihypertensive drugs are required. Treatment with β-blockers should be avoided as they may produce unopposed α-adrenergic vasoconstriction.[43] Postsynaptic α-blockers (eg, terazosin) or mixed α/β blockers (eg, labetalol) can be considered,[44] as can vasodilators with sites of action distal to the adrenergic receptors (hydralazine, calcium channel antagonists).

Substances of Abuse

Alcohol

Excessive alcohol use can increase blood pressure and cause antihypertensive drug resistance in a dose-dependent manner.[45] Several mechanisms have been proposed, including impaired baroreflex activity, sympathetic activation, increased intracellular calcium, cortisol hypersecretion, and reversible disturbances in cellular sodium metabolism.[46–48] Limitation of daily ethanol intake to no more than 1 ounce (30 mL) of 40% ethanol for most men and 0.5 ounces for women and smaller men results in little blood pressure effect.[49] In some cases, blood pressure control is extremely difficult without total abstinence.

Cocaine

The prevalence of recreational drug use mandates that cocaine be considered in all patients presenting for emergency care with hypertensive complaints.[50] Tachycardia and blood pressure elevation are common clinical manifestations of cocaine intoxication.[51] By blocking neuronal reuptake of norepinephrine, cocaine causes neurotransmitter accumulation in the synaptic cleft and results in intense sympathetic activation.[52] Most of these patients do not require antihypertensive drug therapy, but if treatment is necessary, α-adrenergic receptor antagonists, direct vasodilators, calcium channel blockers and combined α/β blockers are logical choices.[52,53] Nitroglycerin and calcium channel antagonists reverse cocaine-induced hypertension and coronary vasoconstriction and are agents of choice for ischemic chest pain in this setting.

Amphetamines

Amphetamines are noncatechol sympathomimetic agents with substantial abuse potential. The cardiovascular complications of amphetamines are comparable to those of cocaine and include hypertension and tachycardia.[54] Methylphenidate has been reported to cause hypertension in children treated for attention deficit disorder.[55] Mescaline has effects very similar to amphetamines and can increase blood pressure.[54] Studies showing the superiority of one antihypertensive strategy over others are lacking.

Antidepressants

Monoamine oxidase inhibitors may cause severe hypertension in patients who consume foods containing tyramine.[56] Although the drugs themselves can exacerbate hypertension by increasing the half-life of norepinephrine at sympathetic nerve terminals, the effect is magnified when amine precursors (dietary tyramine) are present.[57] Of these agents, tranylcypromine is the most likely to raise blood pressure, as opposed to moclobemide and brofaromine, which are the least likely to elevate pressures. α-and combined α/β blockers seem appropriate for initial management.[58,59] Tricyclic antidepressants increase blood pressure in patients with panic disorders[60] or pheochromocytoma.[61] Sustained dose-dependent increases in blood pressure have been reported in patients receiving therapeutic doses of venlafaxine.[62] Episodes of severe hypertension have also been described in patients treated with other antidepressants such as fluoxetine.[63]

Antihypertensive Agents

Volume contracted, high-renin hypertensive patients may experience "paradoxic" blood pressure elevation when diuretics or vasodilators (which further stimulate renin production) are added to their regimens.[64] Central α-2 agonists (clonidine) may cause peripheral vasoconstriction via crossover stimulation of peripheral postsynaptic α-1 receptors,[65] while sympatholytics such as methyldopa[66] may cause transient hypertensive exacerbation before their hypotensive effects become manifest. Rebound or withdrawal hypertension has been associated with the abrupt discontinuation of clonidine and β-blockers (most commonly), but also minoxidil, methyldopa, nifedipine and guanethidine.[67] The likely mechanism of clonidine withdrawal is a rapid resumption of catecholamine production suppressed during therapy.[68] Withdrawal hypertension from β-blockers occurs due to therapy-induced receptor upregulation,[69] and gradual dose tapering avoids this reaction. Although not substantiated, selective β_1 specific blockers[70] or longer acting β-blockers may be associated with this complication less frequently.[71] Concurrent use of clonidine and β-blockers place patients at particularly high risk for rebound hypertension should clonidine be stopped, due to the absence of β_2 vasodilation and unopposed α-receptor stimulation in this setting.[72]

Anesthetics

Ketamine is an anesthetic agent that increases heart rate, systemic arterial pressure, systemic vascular resistance, pul-

Table. Common hypertension-causing drugs

Medication	Mechanism of action	Management
Steroids		
Corticosteroids	Increases sensitivity to catecholamines	Discontinue drug, fluid restriction, diuretics
Mineralocorticoids	Increased exchangeable sodium and blood volume	Discontinue drug, fluid restriction, diuretics
Sex hormones	Sodium retention, volume expansion, increased plasma concentration of angiotensinogen	Discontinue drug, fluid restriction, diuretics
Immunosuppressive agents		
Cyclosporine	Enhanced renal vasoconstriction, volume-dependent hypertension	Discontinue or switch to tacrolimus. Calcium channel antagonists effective
Recombinant human erythropoietin (rHuEPO)	Reduction in nitric oxide-mediated vasodilation and direct vasoconstriction of the resistance arterioles	Dose reduction, fluid removal, conventional antihypertensives and phlebotomy in refractory cases
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Cyclo-oxygenase inhibition reduces vasodilatory prostaglandin synthesis	Discontinue drug, calcium channel blockers and central sympatholytics
Therapeutic sympathomimetic amines	α-adrenergic agonism by postsynaptic receptor binding and/or norepinephrine release from neuronal storage sites	Discontinue drug, postsynaptic α-blockers, combined α/β blockers or vasodilators
Substances of abuse		
Alcohol	Impaired baroreflex activity, sympathetic activation, cortisol hypersecretion, increased intracellular calcium, disturbances in cellular sodium metabolism	Limitation of alcohol intake
Cocaine	Blocks neuronal uptake of norepinephrine causing intense sympathetic activation	α-adrenergic receptor antagonists, direct vasodilators, calcium channel blockers and combined α/β blockers
Antidepressants	Increases the half life of norepinephrine at sympathetic nerve terminals	Alpha- and combined α/β blockers
Antihypertensive agents		
Diuretics or vasodilators	Stimulate renin production	Avoid volume depletion
Clonidine withdrawal	Clonidine withdrawal causes rapid resumption of catecholamine production which was suppressed during therapy	Gradual dose tapering
Beta-blocker withdrawal	Beta blocker-induced receptor upregulation	Gradual dose tapering
Anesthetics		
Ketamine	Increases systemic vascular resistance	Clonidine or α-blockers
Desflurane	Sympathomimetic	Sympatholytics (α-blockers, α/β-blockers, or clonidine)
Miscellaneous agents		
Ergot alkaloids/bromocriptine	Facilitates smooth muscle constriction by increasing cytosolic calcium	Avoid use if possible
Sibutramine	Serotonin-norepinephrine reuptake inhibitor elevates blood pressure through a similar pharmacologic effect on vascular afferent nerves	Discontinue
Glucagon	Sympathomimetic	Sympatholytics (α-blockers, α/β-blockers, or clonidine)
Ginseng	Sympathomimetic	Discontinue
Ephedra	Sympathomimetic	Discontinue

monary arterial pressure, and pulmonary vascular resistance.[73] Desflurane may also cause tachycardia and hypertension in some patients sensitive to sympathetic nervous system stimulation.[74] Many other agents can precipitate hypertension in patients with pheochromocytoma, including fentanyl, other opiates, and neuromuscular relaxants (succinylcholine), as can glucagon used during endoscopic procedures.[75,76] Sympatholytics (α-blockers, α/β-blockers, or clonidine) are usually effective treatments.[77] Although contributing to hypertension in the hospital or procedure lab settings, long-term hypertension has not been reported.

Miscellaneous Agents

Ergot Alkaloids

All natural ergot compounds can cause hypertension by facilitating smooth muscle constriction by increasing cytosolic calcium[78]; the hypertension can be quite severe and may pre-

cipitate myocardial infarctions.[79,80] Bromocriptine, a semisynthetic ergot alkaloid used to treat Parkinson disease and hyperprolactinemia, elevates blood pressure through vasoconstriction and sympathetic nervous stimulation at the ganglionic level.[81,82] Ergot-induced hypertension is more common in patients with previous pregnancy-induced hypertension.[81]

Other Therapeutic Agents

Sibutramine, a serotonin-norepinephrine reuptake inhibitor used to treat obesity, often elevates blood pressure through a similar pharmacologic effect on vascular afferent nerves.[83] Although Sramek et al[84] reported that the addition of sibutramine did not result in blood pressure elevation in obese patients whose hypertension was well controlled by a β blocker, patients receiving sibutramine should have periodic blood pressure monitoring. The drug should be withdrawn if blood pressure increases.

Ginseng has been associated with hypertension.[85] Ephedra-containing dietary supplements (including *ma huang*), widely used for weight loss and increased energy, produce hypertension as their most common adverse effects.[86] The ephedra- and caffeine-containing dietary supplement Metabolife 356 has also been linked to hypertension, sometimes severe and/or acute, and occasionally associated with hypertensive emergencies (intracranial hemorrhage).[87]

Vitamins and their analogues (vitamin A,[88] tretinoin[89]) and mineral micronutrients like iron[90] may exacerbate or cause hypertension following overdose, or with repeated ingestion of supratherapeutic doses.

Antiemetic agents, including metoclopropamide and prochlorperazine, may increase blood pressure transiently in patients treated with cisplatin.[91,92] Additional cases of hypertensive crisis due to metoclopramide have been reported in patients with pheochromocytoma.[93]

Patients who consume ethanol while taking disulfiram are frequently hypertensive, but other symptoms (vomiting) usually inhibit combined ingestion on a recurring basis.[94]

Oral physostigmine has also been reported to increase blood pressure, presumably through central sympathetic activation.[95,96] L-dopa[97] and yohimbine[98] stimulate the sympathetic nervous system at the presynaptic level and cause hypertension.

Hypertension was experienced by 5 to 10% of patients in clinical trials of the disease-modifying antirheumatic drug leflunomide.[99]

Occasionally, peptide hormones (growth hormone,[100] thyroid hormone[101]) can elevate blood pressure through metabolic effects which increase heart rate and myocardial contractility, and through vascular changes resulting in vascular remodeling. Thyrotropin-releasing hormone can raise blood pressure acutely (but not chronically) by increasing systemic vascular resistance rather than cardiac output.[102]

Heavy Metals and Other Toxins

Paint and pesticides are sources of human exposure to heavy metals. A recent study showed that lead can elevate blood pressure both acutely (recent dose) and chronically (cumulative dosing).[103] Thallium,[104] cadmium,[105] and arsenic[106] exposure also may induce hypertension in humans. Venoms of scorpions (especially certain South American species) and black widow spiders can produce severe hypertension by causing a massive discharge of preformed catecholamines into the circulation.[107] Organophosphates in insecticides can elevate blood pressure acutely due to action at nicotinic receptors.[108]

Summary

A variety of exogenous substances can induce transient or sustained hypertension, exacerbate pre-existing hypertension, create resistance to previously effective antihypertensive regimens, and/or precipitate hypertensive emergencies. Knowledge of patient use of, or exposure to, these agents is crucial to avoid unnecessary and expensive tests and/or treatments. While many medications and classes of drugs can have this effect, it is impossible to be all-inclusive in a single writing, and clinicians should take meticulous exposure histories and regularly review new information sources when evaluating hypertensive patients. If contributing drugs or chemicals are identified, discontinuation or avoidance is recommended whenever possible, and appropriate antihypertensive therapy indicated when the offending agent is necessary or cannot be avoided (Table).

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I believe there are more instances of the abridgement of freedom of the people by gradual and silent encroachments by those in power than by violent and sudden usurpations.

—James Madison