Review Paper

Secondary Hypertension: Interfering Substances

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A variety of therapeutic agents or chemical substances can induce either a transient or persistent increase in blood pressure or interfere with the blood pressure–lowering effects of antihypertensive drugs. Some agents either cause sodium retention and extracellular volume expansion or directly or indirectly activate the sympathetic nervous system. Other substances act directly on arteriolar smooth muscle or do not have a defined mechanism of action. Some medications that usually lower blood pressure may paradoxically increase blood pressure, and an increase in pressure may be encountered after their discontinuation. In general, these pressure increases are small and transient; however, severe hypertension involving encephalopathy, stroke, and irreversible renal failure have been reported. Careful evaluation of a patient's drug regimen may identify chemically induced hypertension and obviate unnecessary evaluation and direct to the optimal antihypertensive therapy. The present review summarizes the therapeutic agents or chemical substances that elevate blood pressure and their mechanisms of action. J Clin Hypertens (Greenwich). *2008;10:556–566.* ©*2008 Le Jacq*

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Most patients with hypertension have primary hypertension or, in a relatively few cases, well-known forms of secondary hypertension such as renal disease, renal artery stenosis, or endocrine diseases (hyperaldosteronism or pheochromocytoma). Physicians are less aware of drug-induced hypertension. A detailed medical history should include inquiries concerning foods, poisons, and medications that patients do not consider to be drugs and therefore frequently omit from their history. Identification of the intake of these substances is important; their elimination might obviate the need for unnecessary evaluations or treatments.[1,2]

We review the therapeutic agents or chemical substances that may elevate blood pressure (BP) by different mechanisms of action (Table).

STEROIDS

Hypertension occurs in at least 20% of patients treated with synthetic corticosteroids in a dose-dependent fashion; oral cortisol at dosages of 80 to 200 mg/d can increase systolic BP as much as 15 mm Hg within 24 hours. Cortisol at low dosages has less effect on BP. Glucocorticoid-induced hypertension occurs more often in elderly patients and in patients with a positive family history of primary hypertension.[3] Certain exogenous compounds such as 9-α-fluoroprednisolone and 9-α-fluorocortisol increase BP through mineralocorticoid (MR) receptor activation. Other compounds such as licorice candy and carbenoxolone enhance the conversion of glucocorticoids to mineralocorticoids by inhibiting the enzyme 11 β hydroxysteroid dehydrogenase, thereby activating MR receptors and raising BP. Excess consumption of these compounds may produce arterial hypertension characterized by increased exchangeable sodium and blood

Table. List of Mmedications That May Increase BP

Ingredient	Clinical Use	Notes
Steroids		
Glucocorticoid	Replacement therapy, rheumatic disease, collagen disease, dermatologic disease, allergic state, opthalmic disease, inflammatory bowel disease, respiratory disease, hematologic and neoplastic disease, nephropathies	Dose-dependent sustained increase mainly in systolic BP
Mineralocorticoid		Dose-dependent, sustained increase in BP characterized by hypokalemia, metabolic alkalosis, and suppressed plasma renin activity and aldosterone levels
Licorice	Flavoring and sweetening agent	
Carbenoxolone	Ulcer medication	
9-α-Fluoroprednisolone	Skin ointments, antihemorrhoid cream	
9-α-Fluorocortisol	Ophthalmic drops, nasal sprays	
Ketoconazole	Antimycotic	
Sex hormones		Contraception, replacement therapy in premenopausal women. Severe hypertension has been reported.
Estrogen + progesterone	Contraception, replacement therapy	Mild, sustained BP elevation, more common in premenopausal women. Severe hypertension has been reported.
Androgens	Prostate cancer	Mild dose-dependent sustained increase in systolic BP
Danazol (semisynthetic androgen)	Anabolic effect, endometriosis, hereditary angioedema	
Anesthetics, narcotics		
Ketamine hydrochloride	Anesthetic agent	Transient severe increase in BP has been reported
Fentanyl citrate	Narcotic analgesic and anesthetic agent	
Scopolamine	Preanesthetic medication, motion sickness	
Naloxone hydrochloride	Opioid overdose	Transient BP elevation
Drugs affecting the sympathetic nervous system		
Phenylephrine hydrochloride	Upper respiratory decongestant, ophthalmic drops	Dose-dependent, sustained increase in BP
Dipivalyl adrenaline hydrochloride	Opthalmic drops	Severe hypertension has been reported
Epinephrine (with β-blocker)	Local anesthetic, anaphylactic reaction bronchodilatation, decongestant, antihemorrhoidal treatment	
Phenylpropanolamine	Anorectic, upper respiratory decongestant	
Pseudoephedrine hydrochloride	Upper respiratory decongestant	
Tetrahydrozoline hydrochloride	Opthalmic vasoconstrictor drops	
Naphazoline hydrochloride	Opthalmic vasoconstrictor and nasal decongestant drops	
Oxymetazoline hydrochloride	Upper respiratory decongestant drops	
Caffeine	Analgesia, vascular headache, beverages	Acute transient increase in BP
Herbal products	Complementary and alternative medicine	Mainly relate to dietary supplements that contain ephedra alkaloids
Cocaine	Local anesthetics	Transient severe increase in BP especially when used with β-blockers
Antiemetic agents		
Metoclopramide	Antiemetic	Transient increase in BP in association with cancer
Alizapride	Antiemetic	
Prochlorperazine	Antiemetic	
Other agents		
Smokeless tobacco	Alternative to smoking	
Methylphenidate, demethylphenidate, amphetamine	Attention deficit/hyperactivity disorder	
Yohimbine hydrochloride	Impotence	Acute, dose-dependent increase in BP
Sibutramine	Weight loss	
Clozapine	Antipsychotic agent	
Glucagon	Prevent bowel spasm	Only in patients with pheochromocytoma
Physostigmine	Reverse anticholinergic syndrome	

table continues on next page

Table. List of Mmedications That May Increase BP (continued)

Ingredient	Clinical Use	Notes
Ritodrine hydrochloride	Inhibition of preterm labor	Hypertensive crisis has been reported
Antidepressant agents		
MAOIs	Antidepressive agents	Mainly with sympathomimetic amines and with certain food containing tyramine
Selegiline	Used mainly for Parkinson's disease	
Tricyclic antidepressants	Antidepressive agent	More common in patients with panic disorders
Buspirone	Anxiolytic agent	Mild, dose-dependent increase in BP
Fluoxetine	Antidepressive agent	In combination with selegiline
Thioridazine hydrochloride	Psychotic and depressive disorders	Massive overdose may cause severe hypertension
Carbamazepine	Bipolar disorder and seizures	
Lithium	Manic depressive illness	Acute intoxication can cause severe hypertension
Immunosuppressive agents		
Cyclosporine A	Immunosuppressive agent, prophylaxis of organ rejection, autoimmune disease, dermatologic disorders	Dose-dependent, mild to moderate increase in BP; severe hypertension has been reported
Tacrolimus	Prophylaxis of organ rejection	Produces less hypertension than cyclosporine A
Rapamycin	Prophylaxis of organ rejection	Produces little BP increase
Antineoplastic agents		
Alkylating agents	Antineoplastic agent	
Paclitaxel	Antineoplastic agent	
Cis-diamminedichloroplatinum	Antineoplastic agent	Only during intra-arterial administration
Bevacizumab	A recombinant monoclonal antibody against vascular endothelial growth factor that is used to treat metastatic cancers of the colon, rectum, kidney, and breast	
Sorafenib	Approved for advanced renal cell carcinoma	
Sunitinib	Advanced gastrointestinal stromal tumor and renal cell carcinoma	
Recombinant human erythropoietin	Anemia of renal failure	Dose-related, mild increase, in BP; hypertensive crisis with encephalopathy has been reported
Alcohol	Beverage	Dose-dependent, sustained increase in BP
Disulfiram	Management of alcoholism	Slight increase in BP. Severe hypertension may occur in alcoholic-induced liver disease
NSAIDs	Rheumatic disease	Mild, dose-dependent increase in BP
Heavy metals		
Lead	Industry	
Cadmium	Industry	The association between cadmium exposure and hypertension is equivocal
Arsenic	Industry	
Bromocriptine mesylate	Suppression of lactation and prolactin inhibition in prolactinoma	Severe hypertension with stroke has been reported following the use for suppression of lactation
Amphotericin B	Fungal infections	
Torcetrapib	Cholesteryl ester transfer protein inhibitor that increases high-density lipoprotein cholesterol levels	
Protease inhibitor	Anti–human immunodeficiency virus treatment	

Abbreviations: BP, blood pressure; MAOI, monoamine oxidase inhibitors; NSAIDs, nonsteroidal anti-inflammatory drugs.

volume, hypokalemia with metabolic alkalosis, and suppressed plasma renin and aldosterone levels.[2] Prolonged use of high-dose ketoconazole, an antimycotic agent, may alter enzymatic degradation of steroids, leading to MR-related hypertension.[3] Skin ointments, antihemorrhoidal preparations, ophthalmic drops, and nasal sprays may contain substances with MR activity (9-α-fluoroprednisolone) and substances that activate the sympathetic nervous system. Their excessive use may even cause significant elevation of BP.[2]

SEX HORMONES

Oral contraceptives induce hypertension in approximately 5% of users of combined high-dose compounds that contain at least 50 μg of estrogen and 1 to 4 mg of progestin.[4] The increased pressure is usually minimal, however; rarely, severe hypertensive episodes, including malignant hypertension, may occur. Women with a history of high BP during pregnancy, those with a family history of hypertension, cigarette smokers, obese women, blacks, diabetics, and individuals with renal disease are more susceptible to increases in BP.[2]

No significant association between hypertension and use of progesterone-only pills has been found over 2 to 4 years of follow-up,[5] but this matter has not been addressed by randomized studies. Postmenopausal hormonal replacement therapy (HRT) has minimal if any effect on arterial pressure in normotensive women; rare cases of estrogen-induced hypertension represent an idiosyncratic reaction.[2] Affinito and coworkers[6] showed, using 24-hour ambulatory BP measurements, that HRT can even reduce BP in postmenopausal hypertensive women.[6] HRT use has been associated with increased cardiovascular morbidity and mortality; however, it is no longer recommended unless severe menopausal symptoms are present.[7]

Men receiving estrogen for the treatment of prostate cancer may also exhibit an increase in BP. Danazol, a semisynthetic androgen that is used in the treatment of endometriosis and hereditary angioedema, has been reported to induce hypertension due to fluid retention.[2]

ANESTHETICS AND NARCOTICS

Ketamine hydrochloride, widely used as an anesthetic in children, has been reported to increase arterial pressure. Clonidine, which suppresses sympathetic activity, can reverse the hypertensive response to ketamine.[2]

High-dose fentanyl, is used as an anesthetic agent in valvular and coronary heart surgery, may increase BP.[2] Hypertensive responses to naloxone (opiate antagonist), especially during attempted reversal of narcotic-induced anesthesia in hypertensive patients, have also been reported. Endogenous opioids appear to regulate BP in some hypertensive patients; antagonizing their effect may increase BP.[2]

DRUGS AFFECTING THE SYMPATHETIC NERVOUS SYSTEM

Agents That Directly Activate the Sympathetic Nervous System

Phenylephrine, a sympathomimetic agent with potent vasoconstrictor activity, has been reported to increase arterial pressure following its administration in an ophthalmic solution.[2] The most important factor in the development of hypertension from topically applied phenylephrine is the total dose administered; it appears that infants, because of their immature degradation pathways, are more susceptible than adults. Dipivalyl adrenaline, an adrenaline prodrug used topically in the management of chronic simple glaucoma, can also increase BP in treated hypertensive patients.[2]

The concomitant use of sympathomimetic agents and β-blockers can severely increase arterial pressure because of unopposed α-adrenergic vasoconstriction.[2]

Over-the-Counter Drugs

Most nonprescription anorexics contain combinations of an antihistamine and an adrenergic agonist (usually phenylpropanolamine, ephedrine, pseudoephedrine, or caffeine). All act by potentiating presynaptic norepinephrine release and by directly activating adrenergic receptors. In a recent meta-analysis, Salerno and associates[8] reported that phenylpropanolamine, an active ingredient in most diet aids and many decongestant agents, caused a small but significant increase in systolic BP. The effect was more pronounced with shorter-term administration, higher doses of medication, and immediate-release formulations.[8] Excessive doses may result in severe hypertension and, in rare instances, hypertensive encephalopathy, intracerebral hemorrhage, and death.[2]

AGENTS THAT INDIRECTLY ACTIVATE THE SYMPATHETIC NERVOUS SYSTEM

Caffeine

Caffeine causes a pressor response due to increased sympathetic activity and antagonism of endogenous adenosine.[9] Several investigators have shown by using ambulatory BP monitoring that caffeine may increase BP levels.[10] The caffeine in 2 or 3 cups of coffee can acutely raise BP by as much as 10 mm Hg in patients who are infrequently exposed to it, although the average response is an increase of about 4/3 or 5/3 mm Hg.[9] The reaction to caffeine is more pronounced in men, in those with a positive family history of hypertension, and in blacks.[10] Caffeine may cause persistent BP effects in persons who are regular consumers, even when daily intake is at moderately high levels. In a recent meta-analysis, Noordzij and colleagues[11] found that regular caffeine intake increases BP; however, when ingested through coffee, the BP effect of caffeine is small.[11]

Herbal Products

Popular herbal products have the potential to increase BP and to interfere with antihypertensive treatment.[12] The evidence is anecdotal, and therefore it is impossible to estimate the true incidence of these adverse effects. Several reports have noted that dietary supplements that contain ephedra alkaloids can increase BP.[13] A recent report described a 42-year-old previously healthy man

who developed malignant hypertension and hypertensive retinopathy while taking Hydroxycut, a caffeine-based, ephedra-free herbal supplement.[14] Some herbs can have a significant influence on concurrently administered drugs.[15] Hypertension has also been reported after coadministration of ginkgo and a diuretic thiazide.[12]

Cocaine

Cocaine intoxication and abuse is characterized by adrenergic overactivity associated with increased BP. Cocaine use is associated with acute but not chronic hypertension. Severe hypertension has been reported to occur in persons using cocaine who are taking propranolol, because of unopposed peripheral α-stimulation.[2] Hypertensive encephalopathy secondary to cocaine abuse was reported in a 40-year-old woman who was treated successfully with nitroprusside and captopril.[16] In one small study, isradipine significantly reduced cocaine-induced BP elevation.[17] Cocaine ingestion during pregnancy increases the risk of early placental abruption; BP elevations are less responsive to conventional therapy than is pregnancy-induced hypertension.[2]

Many agents that are not widely used have also been shown to increase BP or interfere with the effects of antihypertensive drugs.

Antiemetic Agents

Antiemetic agents such as metoclopramide, alizapride, and prochlorperazine have been reported to increase BP transiently.[2] Metoclopramide, an antiemetic agent classified as an antagonist of central and peripheral dopamine receptors, has been reported to increase BP transiently in patients treated with cisplatin.[2] The exact mechanism responsible for the rise in BP is unclear. Two other antiemetics, alizapride and prochlorperazine, were found to have similar effects on BP.[2]

Yohimbine Hydrochloride

Yohimbine hydrochloride, an α_2-adrenoceptor antagonist that is approved for treatment of erectile dysfunction, may increase BP.[2] In normal volunteers and in patients with panic disorders, oral administration at doses used clinically may slightly increase BP. However, in hypertensive patients, oral yohimbine was reported to induce a significant increase in mean arterial pressure.[18] Yohimbine increases BP by stimulation of the sympathetic nervous outflow.[19]

Sibutramine

Sibutramine, a novel serotonin and noradrenaline reuptake inhibitor, is an anti-obesity drug. By activating the sympathetic nervous system, the drug may increase heart rate and BP.[20] In obese, hypertensive patients the BP reduction achieved by weight loss may negate the potential BP increase related to the drug.[21] In the recent single-blind lead-in period of the Sibutramine Cardiovascular Outcomes (SCOUT) trial, obese patients with an increased risk of cardiovascular disease were treated with sibutramine plus weight management for 6 weeks. Unexpectedly, the decrease in body weight in these individuals was associated with a significant decrease in BP, despite a significant increase in heart rate.[22] In a combined analysis of 2 placebo-controlled trials, sibutramine treatment did not elicit an increase in BP, even in hypertensive patients.[23] Nevertheless, obese patients being treated with sibutramine should be monitored periodically for changes in BP.

Clozapine

Clozapine is an antipsychotic agent that is used to treat schizophrenic symptoms in patients refractory to classical antipsychotics. This drug may raise BP by sympathetic activation.[2] Several case reports of pseudopheochromocytoma syndrome associated with clozapine have been described.[3] Sympathetic overactivity and BP were normalized upon treatment discontinuation. It is not clear whether long-term use of clozapine may induce hypertension. Lund and colleagues[24] did not find an increased risk of developing hypertension, whereas Henderson and associates reported increased rates of hypertension in patients treated with clozapine.[25]

Nonspecific Agents

Various forms of smokeless tobacco (mainly snuff and chewing tobacco) cause an immediate increase in BP. The increase is in the order of 10 to 20 mm Hg systolic and 6 to 12 mm Hg diastolic. The increase in BP seems to be a direct effect of nicotine that activates the sympathoadrenal axis and contains a high content of sodium and sometimes licorice.[26]

Methylphenidate, dexmethylphenidate, and amphetamine are central nervous system stimulants that are most commonly used in attention deficit/hyperactivity disorder. These agents have the potential to raise BP and induce sustained hypertension.[27,28]

Glucagon may produce a catecholamine-mediated rise in BP in patients with pheochromocytoma.[29] Blocking the α-adrenoceptors with either intravenous phentolamine or oral agents such as

phenoxybenzamine or doxazosin may prevent serious cardiovascular events.

Administration of physostigmine, a centrally acting cholinergic agent, in patients with Alzheimer's disease has been accompanied by a rise in BP, probably due to direct sympathetic activation.[2]

A hypertensive crisis was reported in a pregnant woman who was treated with ritodrine hydrochloride for inhibition of preterm labor. This was related to its inherent pharmacology as a β-mimetic drug.[2]

ANTIDEPRESSANT AGENTS

Monoamine oxidase inhibitors (MAOIs) are used to treat patients with depression. They exert their effects by delaying the metabolism of sympathomimetic amines and 5-hydroxytryptophan and by increasing the store of norepinephrine in postganglionic sympathetic neurons. Hypertensive crisis, the most serious toxic effect of these agents, has been reported more frequently when MAOIs were taken concomitantly with exogenous sympathomimetic amines.[2]

Certain foods containing tyramine, such as cheese (parmiggiano), beer, wine (chianti), snails, chicken liver, yeast, coffee, citrus fruits, avocados, canned figs, broad beans, chocolate, and bananas may interact with MAOIs to cause a hypertensive crisis. There are some reports of MAOIs that cause severe hypertensive reactions even without use of concomitant medications. Among the various MAOIs, tranylcypromine is the most hazardous because of its stimulant action, whereas moclobemide and brofaromine are the least likely to induce a hypertensive reaction.[2] Selegiline, a type B MAOI mainly used for Parkinson's disease. may also increase BP.[3]

Tricyclic antidepressants block the reuptake of the neurotransmitters in the synapse in the central nervous system. There are some reports that these agents increase BP, mainly in patients with panic disorders.[30]

Buspirone, a serotonin receptor type 1α agonist, has also been reported to increase BP.[31] It is speculated that buspirone increases BP by its metabolite 1–2 pyrimidinyl piperazine, which is an α_2-adrenoceptor antagonist and therefore should not be used concomitantly with an MAOI. A small but sustained and dose-dependent increase in arterial pressure seems to occur with other serotonin agonists as well. Venlafaxine has a dose-dependent effect on BP that is clinically significant at high dosages.[32] Episodes of severe hypertension were described in some patients treated with other antidepressant agents such as fluoxetine, fluoxetine plus selegiline, and thioridazine.[2,33]

Carbamazepine used for bipolar depression and seizures may also induce hypertension.[34]

In rare cases, lithium intoxication has been accompanied by definite elevations in BP. The exact mechanism for this phenomenon is not known.[2]

IMMUNOSUPPRESSIVE AGENTS

Cyclosporine A (CyA) is a potent, orally active immunosuppressive drug used in human organ transplantation and in autoimmune diseases. The major adverse effects of cyclosporine are nephrotoxicity and arterial hypertension.

The incidence of cyclosporine-associated hypertension (CAH) varies with the patient population under evaluation. The greatest experience to date has been with patients undergoing organ transplant, with kidney recipients representing the largest single group. Ponticelli[35] found a prevalence of arterial hypertension as high as 81.6% at 1 year after transplantation in 212 cyclosporine-treated renal transplant recipients. The presence of hypertension before transplant, a plasma creatinine level >2 mg/dL at 1 year, and maintenance therapy with corticosteroids were positively associated with CAH. In a large cohort of 1267 kidney transplant patients who received an immunosuppressive regimen based on CyA, usually in association with azathioprine and steroids, the rate of hypertension was 32.7% at 1 year posttransplant.[36]

For patients undergoing bone marrow transplant, the evidence of an excess incidence of hypertension due to CyA appears to be more compelling. Using a randomized prospective design in recipients of bone marrow transplants, Loughran and colleagues[37] reported a 57% incidence of hypertension in CyA-treated patients, compared with a 4% incidence in methotrexate-treated patients. The frequency of CAH in cardiac transplant recipients is approaching 100%, and virtually all patients develop hypertension soon after transplant, independent of renal impairment and irrespective of conventional risk factors associated with CAH.[2]

In liver transplant recipients, CAH is also frequent and occurs in >70% of patients. In liver transplant recipients with CAH, conversion to a low dose of CyA and azathioprine lowers BP.[2] Substitution of CyA with mycophenolate mofetil may improve BP control.[38]

CAH is also common in patients with autoimmune disease treated with CyA. The incidence of new-onset hypertension in patients with autoimmune disease treated with CyA ranges between

11% and 80% and depends on the dose and the duration of treatment.[39] Cyclosporine increases BP after short- and long-term treatment for dermatologic disorders. In psoriatic patients, 4 weeks of treatment with cyclosporine 14 mg/kg/d increased systolic BP by 10% and diastolic BP by 16%.[40] There was a significant correlation between CyA trough levels and diastolic BP. In 26 patients with severe psoriasis, long-term treatment with CyA induced a dose-related increase in mean diastolic BP, and 5 out of 10 patients who were treated with CyA >3 mg/kg/d became hypertensive.[41]

The occurrence of CAH is unrelated to age, sex, and race.[2] While most patients present with mild to moderate asymptomatic BP elevation, a few patients may rapidly develop severe hypertension and encephalopathy. CAH is characterized by a disturbed circadian rhythm with the absence or reversal of the normal nocturnal fall in BP.[42] BP usually decreases after the withdrawal or substitution of cyclosporine immunosuppression but may not remit completely.[42] Calcium antagonists have been used successfully to lower BP, but they can increase cyclosporine blood levels.[43] If necessary, CyA can be continued and multidrug therapy should be used to control CAH.

Tacrolimus, another immunosuppressive agent that inhibits calcineurin, may also induce hypertension. However, it produces less BP elevation than cyclosporin A, and therefore conversion to tacrolimus may be considered in patients with CAH.

Rapamycin and mycophenolate mofetil are immunosuppressive agents that do not inhibit calcineurin and produce little if any nephrotoxicity and hypertension.[44,45]

ANTINEOPLASTIC AGENTS

Several alkylating agents can increase BP. In one series, hypertension (defined as BP >140/90 mm Hg) developed in 15 of 18 patients treated with multiple alkylating agents following autologous bone marrow transplant.[46] Hypertensive reactions associated with paclitaxel treatment have been reported.[47]

Cis-diamminedichloroplatinum is an organic platinum compound with an antineoplastic effect. It has been demonstrated in 4 of 5 patients that intra-arterial administration of Cis-diamminedichloroplatinum produces sustained systemic hypertension for 6 months.[48] This complication has not been observed in patients receiving the drug intravenously. Bevacizumab is a recombinant monoclonal antibody against vascular endothelial growth factor that is used to treat metastatic cancers of the colon, rectum, kidney, and breast. In clinical trials, moderate hypertension that requires antihypertensive treatment was more prevalent in the bevacizumab-treated groups than in the placebo group. The incidence of severe hypertension (BP >200/100 mm Hg) was more than 3- to 5-fold higher in the bevacizumab groups compared with the placebo groups.[49,50] The mechanism for hypertension in the presence of antiangiogenic therapy appears to be related to the decrease in nitric oxide production caused by vascular endothelial growth factor blockage. Furthermore, a reduction in the density of microvessels in tissues and organs may be another consequence of angiogenesis inhibition that contributes to increased vascular resistance and hypertension. BP monitoring every 2 to 3 weeks is recommended for patients receiving bevacizumab therapy. Use of monotherapy or combination antihypertensive therapy has generally been successful in managing the BP elevations.

Sorafenib, a multikinase inhibitor of tumor-cell proliferation and angiogenesis that was recently approved for advanced renal cell carcinoma[51] also can increase BP. In the recent Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET), treatment-related hypertension was reported in 17% of the patients. Grade 3 or 4 hypertension was reported in 4% of the sorafenib-treated patients compared with <1% in the controls. Sunitinib, an orally administered small molecule that inhibits multiple receptor tyrosine kinases, was recently approved for use in advanced gastrointestinal stromal tumor and renal cell carcinoma. One of the reported adverse events of the drug is hypertension. In one of the studies, grade 3 to 4 hypertension was observed in 4% of the sunitinib-treated patients vs none in the placebo-treated group.[52]

RECOMBINANT HUMAN ERYTHROPOIETIN

Recombinant human erythropoietin (r-HuEPO) is effective in correcting the anemia of patients with end-stage renal failure and in treating patients with malignancies.[53] The most frequent adverse effect of r-HuEPO is the development or exacerbation of hypertension.[2] r-HuEPO can lead to an increase in BP that appears to be dose-related. Systemic hypertension has been reported to develop, or to worsen, in 20% to 30% of patients treated with r-HuEPO worldwide.[54] Hypertension may develop in some patients as early as 2 weeks and in others as late as 4 months after the start of r-HuEPO treatment.[2] Hypertension has not proved to be a serious

general problem in the r-HuEPO–treated patient; however, hypertensive crisis with encephalopathy has been reported.[55]

Several risk factors for the development or worsening of hypertension after r-HuEPO therapy have been identified. They include the presence of preexisting hypertension, rapid increase in hematocrit, a low baseline hematocrit before r-HuEPO administration, high doses and intravenous administration, the presence of native kidneys, a genetic predisposition to hypertension, and possibly younger age.[56] By optimizing dialysis treatment, paying close attention to volume regulation, and giving r-HuEPO subcutaneously and in a fashion to increase hematocrit gradually, the occurrence of hypertension can be minimized.[56]

The hypertension associated with r-HuEPO has not generally been too difficult to control. The BP can usually be controlled with a combination of fluid removal with dialysis and conventional antihypertensive therapy. If these measures are unsuccessful, the dose of r-HuEPO should be lowered or therapy should be withheld for several weeks. Phlebotomy of 500 mL of blood may rapidly lower BP in refractory patients.[2]

ALCOHOL

Excessive alcohol use has clearly been shown to raise BP and can also increase resistance to antihypertensive therapy.

Apart from the acute effects of alcohol, an increased prevalence of hypertension has been shown in heavy drinkers.[57,58] In the Australian Risk Factor Prevalence Study,[58] 7% of the prevalence of hypertension was attributed to alcohol consumption, whereas in the Kaiser-Permanente Study,[57] the rate for men was 11%. It was found that the greater the quantity of alcohol consumption, the higher the prevalence of hypertension.[2]

The BP effects of alcohol are independent from obesity, salt intake, cigarette smoking, and potassium intake, and there is a dose-response relationship for the hypertensive effects of alcohol. In a prospective cohort study of 3900 Japanese men, Yoshita and associates[59] found that annual systolic BP increase was greater in those who consumed ≥300 g/wk of alcohol, corresponding to 13 glasses of wine (240 mL each), 13 bottles of beer (633 mL each), or 26 shots of whiskey (35 mL each), than in nondrinkers. Baseline diastolic BP was associated with alcohol consumption and was significantly higher in drinkers consuming ≥200 g/wk than in nondrinkers. Therefore, moderation of alcohol intake is recommended as an initial therapy for mild hypertension. A reasonable approach is to limit alcohol consumption to <200 g/wk.

DISULFIRAM

Disulfiram is commonly used as a pharmacologic adjunct in the treatment of alcoholism. Administration of 500 mg/d of disulfiram for 2 to 3 weeks has been reported to increase BP slightly. A low dosage of 125 mg/d of this agent may also increase BP. It seems that changes in peripheral or central noradrenergic activity are responsible for the increase in arterial pressure.[2]

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Nonsteroidal anti-inflammatory drugs (NSAIDs) can induce an increase in BP and interfere with antihypertensive treatment, nullifying its effect.[2] Meta-analyses from the early 1990s have demonstrated that NSAID use produces a clinically significant increase in mean BP of 5 mm Hg.[2] Elderly patients, those with preexisting hypertension, patients with diabetes mellitus, salt-sensitive patients, patients with renal failure, and those with renovascular hypertension are more susceptible to develop hypertension when treated with NSAIDs.[60]

NSAIDs may interfere with the action of some antihypertensive agents, such as diuretics, β-blockers and angiotensin-converting enzyme inhibitors, but do not interact with calcium antagonists and central-acting drugs.

NSAIDs vary considerably in their effect on BP. Armstrong and Malone[61] found, among the various NSAIDs, that indomethacin, naproxen, and piroxicam were associated with the greatest increase in BP.[61] They also reported that among the selective NSAIDs, rofecoxib was more likely than celecoxib to raise systolic BP. In a recent meta-analysis, Aw and colleagues[62] showed that selective COX-2 inhibitors increase BP more than the nonselective agents. Unlike these findings, the research of Wang and associates[63] showed in a population-based cohort analysis that there were similar hazard rates of incident hypertension in celecoxib and nonselective NSAIDs users. It seems that the greater impact of COX-2 inhibitors on BP is driven primarily by the effects of rofecoxib. Several studies showed that rofecoxib, which is off the market, increases BP more than celecoxib.[62,64] A 2005 study by Sowers and associates[64] showed that at equally effective doses for osteoarthritis management, treatment with rofecoxib but not celecoxib or naproxen induced a significant increase in 24-hour systolic

BP from 130.3±1.2 to 134.5±1.4 mm Hg. It is noteworthy that celecoxib may also increase BP in a dose-dependent way. In the studies that compared the efficacy and safety of celecoxib with placebo in reducing the rate of colorectal cancer, patients who received celecoxib 400 mg twice daily exhibited a 5.2-mm Hg increase in systolic BP after 3 years.[65] No change in BP was observed in those who took the drug once daily or in the usual dosages of 100 to 200 mg/d. Similar findings were described by Izhar and coworkers,[66] who studied the effects of celecoxib and diclofenac on ambulatory BP in a double-blind crossover study. Mean 24-hour systolic BP was significantly increased by diclofenac (4.2 mm Hg) compared with celecoxib (0.6 mmHg). The authors felt that these differences were attributable in part to the once-daily dosing of celecoxib compared with the twice-daily dosing of diclofenac. Low-dose aspirin has no effect on BP control in hypertensive patients. It is wise to balance the risk of an increase in BP against the expected benefit of treatment with an NSAID. In patients who receive NSAIDs, calcium antagonists would appear to be a preferred choice to other antihypertensive agents.[67]

HEAVY METALS

Epidemiologic studies have confirmed that environmental exposure to lead is associated with an increased risk of hypertension.[68]

Even at low levels of exposure (40 μg/dL), blood lead level was positively associated with both systolic and diastolic BP and risks of hypertension among women aged 40 to 59 years. The relationship between blood lead level and BP levels was most pronounced in postmenopausal women.[68] History of lead exposure influences hypertension and elevated BP during pregnancy.[69] These results provide support for continued efforts to reduce lead levels in the general population, especially women.

A retrospective study of 311 male workers in an alkaline battery factory indicated a possible relationship between exposure to cadmium oxide and the development of hypertension.[2] In a study published in 2000, environmental exposure to cadmium was not associated with higher conventional BP or 24-hour ambulatory BP measurements or with increased risk of hypertension.[70]

It has been suggested that arsenic exposure also may induce hypertension in humans.[71]

OTHER AGENTS

Bromocriptine

Bromocriptine mesylate is commonly used for prolactin inhibition and suppression of puerperal lactation. Though bromocriptine often has a hypotensive effect, severe hypertension with subsequent stroke has been reported in the postpartum period.[72] Patients with pregnancy-induced hypertension are at increased risk for the development of hypertension. The suppression of lactation is no longer a US Food and Drug Administration–approved use for bromocriptine.

Amphotericin B

Amphotericin B is the mainstay of therapy for serious fungal infections. A few cases of severe hypertension associated with the use of amphotericin B deoxycholate have been reported in the literature, and one case report of hypertension associated with a lipid-containing preparation of the medication has been described.[3]

Anti–Human Immunodeficiency Virus Treatment

Metabolic changes caused by antiretroviral therapy may increase the risk of coronary heart disease.[73] Glass and associates[73] evaluated changes in the prevalence of cardiovascular risk factors and 10-year risk of coronary artery disease in a large cohort of human immunodeficiency virus (HIV)–infected individuals. Hypertension was reported in 26.1% of the infected individuals.

Among 444 patients who initiated highly active antiretroviral therapy, 83 exhibited an increase in systolic BP of ≥10 mm Hg, 33 exhibited an increase in diastolic BP of ≥10 mm Hg, and 11 patients had a new diagnosis of hypertension confirmed by a new antihypertensive treatment. Patients receiving lopinavir/ritonavir had the highest risk of elevated BP (odds ratio, 2.5; $P<.03$) compared with efavirenz-based regimens. Elevated BP was least likely to develop in patients receiving atazanavir. The effect of the treatment on BP was mainly mediated through an increase in body mass index. The impact of antiretroviral medications on cardiovascular disease risk factors will increasingly influence treatment decisions.[74]

One case report of severe hypertension and renal atrophy associated with the protease inhibitor indinavir has been described.[75] Hypertensive crisis secondary to phenylpropanolamine interacting with triple-drug therapy for HIV prophylaxis has also been reported.[76] In addition, potential drug interactions exist between antiretroviral medications, particularly the protease inhibitors and calcium antagonists.[77]

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