Iatrogenic and Drug-Induced Hypertension

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INTRODUCTION

A variety of drugs and chemical substances have been shown to elevate blood pressure (BP). Most often, the increase in BP is transient and of questionable clinical significance. However, more sustained hypertension and even accelerated hypertensive cardiovascular disease have occasionally been documented to occur after exposure to certain chemical substances. Of note, a variety of drugs also make “essential” hypertension more resistant to antihypertensive therapy. An accurate and detailed medical history should, therefore, include specific inquiries concerning foods, poisons, and medications. This is particularly important with regard to such things as over-the-counter drugs, nutritional supplements, diets, and health foods, which are often not considered to be drugs and, therefore, are frequently omitted from the history.

Identification of such substances is important because their elimination can obviate the need for unnecessary, costly, and potentially dangerous evaluations and/or treatments. When drug- or chemical-induced hypertension is identified, discontinuation of the causative agent should be recommended. When it is not possible to discontinue agents that cause hypertension, institution of appropriate antihypertensive treatment is indicated. In the absence of specific treatment guidelines for drug-induced hypertension, the recommended initial antihypertensive therapy should be directed to neutralize the specific mechanism causing hypertension (Table 1).

STEROIDS

Corticosteroids

Hypertension occurs in about 20% of patients treated with high doses of synthetic corticosteroids. Oral cortisol increases BP in a dose-dependent fashion. At a dose of 80–200 mg/day, the peak increases in systolic pressure are of the order of 15 mmHg. This increase in BP is apparent within 24 hours. The mechanism of glucocorticoid (GC)-induced hypertension remains uncertain and it seems to be multifactorial. GC-induced hypertension occurs often in elderly patients and is more common in patients with positive family history of essential hypertension. Hemodynamically, corticosteroids increase BP through increasing circulatory volume, cardiac output, and peripheral resistance. Certain exogenous compounds such as liquorice, phenylbutazone, carbenoxolone, 9-α-fluoroprednisolone, and 9-α-fluorocortisol have mineralocorticoid activity and, when ingested in excessive quantities, may produce arterial hypertension.
characterized by the clinical picture of “pseudohyperaldosteronism” with increased exchangeable sodium and blood volume, hypokalemia with metabolic alkalosis, and suppressed plasma renin and aldosterone levels. Prolonged use of high-dose ketoconazole may alter enzymatic degradation of steroids, leading to mineralocorticoid-related hypertension. Skin ointments, antihemorrhoidal preparations, ophthalmic drops, and nasal sprays may contain substances with mineralocorticoid activity (9-α-fluoroprednisolone) and sympathetic amines. Their excessive use may even cause severe arterial hypertension. Discontinuation of these substances is recommended to lower BP. However, when steroid treatment is mandatory, a diuretic is the drug of choice, because volume overload is the main mechanism by which steroids raise BP; careful monitoring of potassium is necessary.

**Sex Hormones**

Oral contraceptives (OCs) induce hypertension in approximately 5% of users of high-dose compounds that contain at least 50 mg estrogen and 1 to 4 mg progestin, and small increases in BP have been reported even among users of modern low-dose formulations. Women with a history of high BP during pregnancy; those with a family history of hypertension; cigarette smokers; those who are obese, black, or diabetic; and those with renal diseases may respond with a greater increase in BP. Compared with women who had never used OCs, users of OCs have an increased risk of developing hypertension (risk ratio = 1.8; 95% CI = 1.5–2.3). However, only in a small percentage could hypertension be attributed to OC use. Risk of hypertension decreased quickly with cessation of OCs, and past users appeared to have only a slightly increased risk. The increase in BP is usually minimal; however, severe hypertensive episodes, including malignant hypertension, have been reported. Postmenopausal estrogen replacement therapy (ERT) decreases BP slightly, and rare cases of estrogen-induced hypertension represent an idiosyncratic reaction to ERT. Cessation of ERT is recommended when hypertension develops. However, if ERT should be continued, a diuretic is the most appropriate treatment because the contraceptives estrogen and androgen increase BP via fluid retention.

Men receiving estrogen to treat prostatic cancer may also exhibit an increase in BP.

Danazol, a semisynthetic androgen that is used to treat endometriosis and hereditary angioedema, was reported to induce hypertension through fluid retention.
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ANESTHETICS AND NARCOTICS

Ketamine hydrochloride has been reported to severely increase BP. In one study, clonidine that suppresses sympathetic activity was effective in reducing the hypertensive response to ketamine.

Desflurane may induce hypertension via stimulation of the sympathetic nervous system. Sympatholytic agents such as $\alpha$-blockers and $\alpha+\beta$ blockers may lower BP.

Sevoflurane may increase BP during anesthesia. Treatment with clonidine or a combination of diltiazem and nicardipine may blunt the BP increase.

The simultaneous use of vasoconstrictors (felypressin) with topical cocaine can result in severe hypertension. At least one case was treated successfully with labetalol.

Hypertensive responses to naloxone (opiate antagonist), especially during attempted reversal of narcotic-induced anesthesia in hypertensive patients, have also been reported. Naloxone seems to acutely reverse the antihypertensive effects of clonidine and can thereby cause an acute hypertensive emergency.

DRUGS AFFECTING THE SYMPATHETIC NERVOUS SYSTEM

Phenylephrine, a sympathomimetic agent with a potent vasoconstrictor activity, has been reported to severely increase BP following its administration in an ophthalmic solution. Dipivalyl adrenaline, an adrenaline prodrug used topically in the management of chronic simple glaucoma, can also increase BP in treated hypertensive patients.

The concomitant use of sympathomimetic agents and $\beta$-blockers can severely increase BP because of unopposed $\alpha$-adrenergic vasoconstriction. The substitution of $\alpha$-blockers or agents such as labetalol or carvedilol, which block both $\alpha$- and $\beta$-adrenergic receptors, should prevent this detrimental reaction.

Antiemetic agents such as metoclopramide, alizapride and prochlorperazine have been reported to increase BP transiently in patients treated with cisplatin.

Yohimbine hydrochloride—an $\alpha_2$-adrenoceptor antagonist that is approved (but of questionable efficacy) for treatment of impotence—may significantly increase BP in hypertensive patients. Yohimbine should be avoided or used intermittently only in hypertensive patients and in those undergoing concurrent treatment with tricyclic antidepressants.
Glucagon may induce severe hypertension in patients with pheochromocytoma. Blocking the α-adrenoceptors by either intravenous phentolamine or oral agents such as phenoxybenzamine or doxazosin may prevent catastrophic cardiovascular events.

Cocaine intoxication is characterized by α-adrenergic overactivity often associated with increased BP. Cocaine use is associated with acute but not chronic hypertension. Severe hypertension has been reported to occur in subjects treated with propranolol. Most patients with cocaine-related hypertension do not require pharmacological therapy, but if treatment is necessary, α-adrenergic receptor antagonists would seem a logical choice for initial treatment. β-Blockers can be useful in the management of cardiac dysrhythmias, but they should be used with caution because of the possibility of exacerbating hypertension resulting from unopposed α-receptor activity. Nitroglycerin and verapamil reverse cocaine-induced hypertension and coronary arterial vasoconstriction and therefore are the agents of choice in treating patients with cocaine-associated chest pain. One case of hypertensive encephalopathy secondary to cocaine abuse was treated successfully with nitroprusside and captopril.

**Sibutramine**

Sibutramine is a novel serotonin and noradrenaline reuptake inhibitor anti-obesity drug. Sibutramine reduces food intake by enhancing the physiological response of post-ingestive satiety and increases energy expenditure. By activating the sympathetic nervous system, the drug increases heart rate and BP in obese normotensive subjects. In obese patients whose hypertension is well controlled with a β-blocker or angiotensin-converting enzyme (ACE) inhibitor, sibutramine achieves weight loss without compromising good BP control. It seems that in obese hypertensive patients the BP reduction achieved by weight loss negates the potential BP increase related to the drug. Nevertheless, obese patients being treated with sibutramine should be monitored periodically for changes in BP. If BP becomes elevated, sibutramine should be withdrawn.

**Clozapine**

Clozapine is an antipsychotic agent that is used for schizophrenic symptoms in patients refractory to classical antipsychotics. This drug may raise BP by sympathetic activation. Several case reports of pseudopheochromocytoma syndrome associated with clozapine have been described. BP and sympathetic overactivity were normalized upon
treatment discontinuation. In one case, nifedipine controlled clozapine-induced hypertension. However, $\alpha$-adrenergic receptor antagonists would seem a more appropriate choice for initial treatment.

**IMMUNOSUPPRESSIVE AGENTS**

Cyclosporin A—a potent, orally active immunosuppressive drug—may induce arterial hypertension. The incidence of cyclosporin-associated hypertension (CAH) varies with the patient population under evaluation. The greatest experience to date has been with patients undergoing organ transplantation, with kidney recipients representing the largest single group.

However, CAH is also common in patients with autoimmune disease and dermatologic disorders. The risk of CAH is unrelated to sex or race, but it is dose-related and it increases with age of the patient and with preexisting hypertension or high serum creatinine levels. Although most patients present with mild to moderate asymptomatic BP elevation, others may rapidly develop severe hypertension and encephalopathy. BP usually falls after the withdrawal or substitution of cyclosporine immunosuppression but may not remit completely. Unfortunately, it is often not possible to discontinue therapy. Calcium antagonists have been used successfully but they can increase cyclosporin blood levels. ACE inhibitors, labetalol, $\beta$-blockers, clonidine, and diuretics are also effective in some patients. Diuretic therapy should be used with caution because of the risk of prerenal azotemia and electrolyte abnormalities. Usually, multidrug therapy is necessary to control CAH.

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

Rapamycin, a novel immunosuppressive agent that does not inhibit calcineurin, has not been reported to produce nephrotoxicity and/or hypertension.

**OVER-THE-COUNTER DRUGS**

Most nonprescription anorexics contain combinations of an antihistamine and an adrenergic agonist (usually phenylpropanolamine [PPA], ephedrine, pseudoephedrine, or caffeine). All act by potentiating presynaptic norepinephrine release and by directly activating adrenergic receptors. $\alpha$-Adrenergic intoxication induced by nasal decongestant and
cough medications containing massive doses of oxymetazoline hydrochloride, phenylephrine hydrochloride, and ephedrine hydrochloride has been reported to result in severe hypertension. Labetalol may be an effective treatment in these cases.

Until recently, PPA was the active ingredient in most diet aids and many decongestant agents and was also used as a substitute for amphetamine. Use of excessive doses may result in severe hypertension.

Caffeine can acutely and transiently increase BP by increasing peripheral resistance. The reaction to caffeine is more pronounced in males than females, and in those with a positive family history of hypertension than in those with a negative family history. Concomitant medications, such as monoamine oxidase inhibitors (MAOIs), antihypertensive drugs, OCs, and nonsteroidal anti-inflammatory drugs (NSAIDs) seem to increase the risk of hypertension.

**ANTIDEPRESSANT AGENTS**

MAOIs can induce severe hypertension when patients consume foods containing tyramine. However, there are some reports of MAOIs causing severe hypertensive reaction even without use of concomitant medications. Among the various MAOIs, tranylcypromine is the most hazardous, whereas moclobemide and brofaromine seem to be the least likely to induce hypertensive reaction. These drugs exert their effects by delaying the metabolism of sympathomimetic amines and 5-hydroxytryptophan, and by increasing the store of norepinephrine in postganglionic sympathetic neurons. α-Adrenergic receptor antagonists would seem an appropriate choice for initial treatment.

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.

Buspirone, a serotonin receptor type 1α agonist, has also been reported to increase BP. It is speculated that buspirone increases BP by its metabolite 1-2 pyrimidinyl piperazine which is an α2-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 doses. Episodes of severe hypertension were described in patients treated with other antidepressant agents such as fluoxetine, fluoxetine plus selegiline, and thioridazine.
ANTINEOPLASTIC AGENTS

Several alkylating agents can increase BP. In one series, 15 of 18 patients treated with multiple alkylating agents following autologous bone marrow transplantation developed hypertension. Hypertensive reactions associated with paclitaxel treatment has been reported.

RECOMBINANT HUMAN ERYTHROPOIETIN

Recombinant human erythropoietin (r-HuEPO) has revolutionized the treatment of anemia in renal failure patients, both in the pre- and postdialysis phase. Not only does the treatment improve well-being, but it also positively influences cardiac function and permits cardiac hypertrophy to regress. However, r-HuEPO therapy can lead to an increase in BP. The increase in BP associated with r-HuEPO therapy appears to be dose-related. Systemic hypertension has been reported to develop, or to worsen, in 20–30% of patients treated with r-HuEPO worldwide. In hemodialysis patients with systemic hypotension, r-HuEPO usually induces a 10% increase in BP, with no significant change in the frequency of hypotensive episodes. 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.

In general, hypertension has not proved to be a serious general problem in the r-HuEPO-treated patient; however, few cases of hypertensive crisis with encephalopathy have been reported.

Several risk factors for the development, or worsening, of hypertension after r-HuEPO therapy have been identified. They include the presence of pre-existing hypertension, rapid increase in hematocrit, a low baseline hematocrit before r-HuEPO administration, high doses and intravenous route of administration, and the presence of native kidneys. There are several potential mechanisms by which r-HuEPO therapy may increase BP in hemodialysis patients. They include increased blood viscosity; the loss of hypoxic vasodilation; the activation of neurohumoral systems (catecholamines, the renin-angiotensin system); and especially a direct vascular effect. This last mechanism is supported by several studies, and many factors may be involved in its pathogenesis (an increased cell calcium uptake; an imbalance in local vasoactive agents, with increased synthesis of ET-1; a mitogenic effect; and a platelet-dependent mechanism). By optimizing dialysis treatment, paying close attention to volume regulation, giving r-HuEPO subcutaneously and in a fashion to increase hematocrit gradually, the occurrence of BP increases can be minimized.
Hemodynamically, r-HuEPO increases BP by a marked increase in peripheral resistance associated with only a mild decrease in cardiac output. Vasodilators such as calcium antagonists, and $\alpha$-adrenergic receptor antagonists should therefore be effective in lowering BP. Diuretics, ACE inhibitors, and angiotensin type 1 receptor antagonists may be less effective because blood volume has been shown to be unchanged, and both plasma renin activity and angiotensin II are suppressed in r-HuEPO-treated patients. The hypertension associated with r-HuEPO has not generally been too difficult to control. In one study, 42% of the patients with r-HuEPO-induced hypertension had their BP controlled with a single agent. BP can usually be managed 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 held for several weeks. Phlebotomy of 500 mL of blood may rapidly lower BP in refractory patients.

**BROMOCRIPTINE**

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

**DISULFIRAM**

Disulfiram is commonly used as a pharmacologic adjunct in the treatment of alcoholism. Administration of 500 mg/day of disulfiram for 2 to 3 weeks has been reported to increase BP slightly. A low dose of 125 mg per day 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.

**ALCOHOL**

Excessive chronic alcohol use has clearly been shown to raise BP and can also increase resistance to antihypertensive therapy. Pathogenesis of alcohol-related hypertension seems to be multifactorial and related to direct vasculotoxicity, sympathetic activity, salt water logging, and activation of the renin angiotensin system.

The BP effects of alcohol are independent from obesity, salt intake, cigarette smoking, and potassium intake. There is a dose–response rela-
tionship for the hypertensive effects of alcohol. Abstinence or at least moderation of alcohol intake is recommended as an initial therapy for mild hypertension. A reasonable approach is to limit daily alcohol consumption to no more than approximately 1–2 ounces of alcohol.

**NONSTEROIDAL ANTI-INFLAMMATORY DRUGS**

NSAIDs can induce an increase in BP and interfere with antihypertensive treatment, nullifying its effect. Two meta-analyses have demonstrated that, after pooling data drawn from published reports of randomized trials of younger adults, NSAID use produces a clinically significant increment in mean BP of 5 mmHg. Recent NSAID users had a 1.7-fold higher risk of requiring the initiation of antihypertensive therapy compared with nonusers; NSAID users also had a 40% increased risk of receiving a diagnosis of hypertension compared with nonusers. Elderly patients, those with pre-existing hypertension, salt-sensitive patients, patients with renal failure and patients with renovascular hypertension are at a higher risk to develop severe hypertension when treated with NSAIDs. The mechanisms whereby NSAIDs raise BP are not fully understood. Inhibiting the synthesis of prostaglandins from arachidonic acid via cyclooxygenase (COX)-1 and COX-2, the 2 isoforms of COX, is probably the main mechanism of action. Interference with both the control of vascular resistance and the regulation of extracellular volume homeostasis has been incriminated, but several other putative mechanisms such as moderation of adrenergic activity or resetting of the baroreceptor response may also be involved. NSAIDs may interact with some antihypertensive agents such as diuretics, beta-blockers and ACE inhibitors but do not interact with calcium antagonists and central acting drugs, the antihypertensive efficacy of which is apparently unrelated with production of PGs. NSAIDs vary considerably in their effect on BP. Stratification by NSAID type revealed that indomethacin, piroxicam and naproxen were associated with the largest increases in BP, whereas sulindac and aspirin have little effect on BP. Low dose aspirin has no effect on BP control in hypertensive patients. The new orally-effective specific COX-2 inhibitors, rofecoxib and celecoxib, increase BP in a dose-dependent manner as the traditional NSAIDs. However, there is evidence that patients receiving celecoxib experience less destabilization of BP compared with those receiving rofecoxib. Because COX-2 inhibitors are usually given for a prolonged period of time, the risk of an increase in BP must be assessed against the expected benefit of treatment. In patients who take NSAIDs, calcium antagonists would appear to be a preferred choice to other antihypertensive agents.
HEAVY METALS

Several studies show that cumulative exposure to lead, even at low levels sustained by the general population, may increase the risk of hypertension. Some reports suggest that arsenic or cadmium exposure also may induce hypertension in humans. However, in a recent study, environmental exposure to cadmium was not associated with higher conventional BP or 24-hour ambulatory BP measurements.

SCORPIONS AND BLACK WIDOWS

Venoms of scorpions (especially the South American species) and black widows commonly produce a clinical picture of profuse perspiration, lacrimation, vomiting, convulsion, and cardiovascular collapse. However, occasionally hypertension and bradycardia occur. Hypertension is mediated by a massive discharge of catecholamines into the circulation produced by the venom, and therefore \( \beta \)- or \( \alpha \)-blockade is effective in this condition.

AMPHOTERICIN B

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

ANTI-HIV TREATMENT

One case report of severe hypertension and renal atrophy associated with the protease inhibitor indinavir has been described. Hypertensive crisis secondary to phenylpropanolamine interacting with triple-drug therapy for HIV prophylaxis has also been reported. Additionally, potential drug interactions exist between antiretroviral medications, particularly the protease inhibitors and antihypertensive medications.

CONCLUSIONS

A myriad of therapeutic agents or chemical substances can induce either transient or sustained hypertension, exacerbate well-controlled hypertension, or antagonize the effects of antihypertensive therapy. Careful evaluation of a patient’s drug regimen may identify so-called chemically induced hypertension and prevent or minimize the need for lifelong antihypertensive therapy. Whenever chemically induced hyper-
tension has been identified, the causative agent should be discontinued. However, when discontinuation is not possible, institution of appropriate and targeted antihypertensive therapy is indicated. In the absence of specific treatment guidelines for drug-induced hypertension, the recommended initial antihypertensive therapy should be directed toward neutralizing the specific mechanism by which the chemical agent causes hypertension.

**SUGGESTED READINGS**

15. Sibutramine: new preparation. Slight weight loss; but also a slight rise in blood pressure... Prescrire Int 2001;10:140–145.