Hypertension Curriculum Review

Donald G. Vidt, MD, Section Editor

Drug Interactions and Drugs That Affect Blood Pressure

William J. Elliott, MD, PhD

Many antihypertensive drugs have important interactions with drugs used for different purposes; when these are used concomitantly, adverse effects on blood pressure can result. Fortunately, in recent years, the drug development process has generally discouraged the approval and marketing of antihypertensive drugs with this problem, although some anomalies still exist (eg, telmisartan + digoxin). Physicians who work in emergency departments are more familiar with illicit or unregulated drugs that affect blood pressure; chief among these are cocaine and other opioids, and methylphenidate and its congeners. The most important prescription drugs that affect blood pressure are the nonsteroidal anti-inflammatory drugs (including selective inhibitors of the second isoform of cyclooxygenase) and steroids. Phenylpropanolamines, some antidepressants, and sibutramine can often be avoided, as they raise blood pressure in a significant proportion of those who take them. Conversely, the hypertensive effects of calcineurin inhibitors and erythropoietin are most commonly overcome by increasing the intensity of antihypertensive drug treatment, since these drugs are essentially unavoidable in most patients who receive them.
(J Clin Hypertens. 2006;8:731–737)

From the Department of Preventive Medicine, Rush Medical College of Rush University at Rush University Medical Center, Chicago, IL
Address for correspondence:
William J. Elliott, MD, PhD, Professor of Preventive Medicine, Internal Medicine and Pharmacology, Department of Preventive Medicine, Rush Medical College of Rush University at Rush University Medical Center, 1700 West Van Buren Street, Suite 470, Chicago, IL 60612
E-mail: welliott@rush.edu

www.lejacq.com **ID: 5939**

There are two major ways that drug interactions can affect blood pressure (BP) control. The first, which is fortunately much less common than it was 20 years ago, is the use of an antihypertensive that has a significant drug–drug interaction with another drug, typically being used for a different purpose. The second general problem, which is much more common today, is the concomitant use of drugs that raise BP.

IMPORTANT DRUG INTERACTIONS FOR ANTIHYPERTENSIVE DRUGS

Role of the Cytochrome P450 System

Some, but certainly not all, important drug interactions for antihypertensive drugs can be attributed to the sharing of metabolic pathways with other drugs, either inducing or inhibiting the metabolism of the antihypertensive drug. Most of these effects are mediated through the hepatic cytochrome P450 (CYP) system, a superfamily of mixed-function oxidases derived from at least 481 known genes. These are divided into 74 families (denoted by the number after CYP), of which 14 have been found in mammals. The 20 subfamilies are denoted by a capital letter after the designation for the family (eg, CYP3A, which is responsible for about 40%–60% of traditional-type hepatic drug–drug interactions), followed by another capital letter that denotes the specific enzyme (or closely-related enzymes) of interest. Many of the specific enzymes that are affected (and affect) older antihypertensive drugs have been reasonably well identified. Probably the best studied of these drugs is propranolol, which is potentiated by agents metabolized by CYP2D6, CYP1A2, and CYP2C19 (among others), and which itself can affect both hepatic blood flow and other cytochrome enzymes. Because of the many, varied, and sometimes

unpredictable interaction of the cytochrome system and older drugs, there has been a strong tendency in the past 20–30 years to focus on the development of new drugs with few, if any, metabolic effects mediated by the cytochrome system. As a result, very few antihypertensive drugs introduced since about 1990 have clinically troublesome drug interactions that can be linked to CYP450 metabolism, since many such interactions can be predicted by in vitro testing.

Diuretics

Because diuretics are excreted renally and increase both natriuresis and diuresis, they can, as a class, interfere with (and be interfered somewhat by) other drugs that are primarily handled by the kidney. All diuretics can increase digitalis toxicity (probably through hypokalemia) and lithium toxicity, and all can have their BP-lowering and diuretic effects reduced by nonsteroidal anti-inflammatory drugs (NSAIDs). Ethanol and central nervous system depressants are noted in the prescribing information for all diuretics to potentiate their orthostatic hypotensive effects. Hypokalemia is a complication of concomitant use of diuretics and corticosteroids, corticotropin (formerly adrenocorticotropic hormone, or ACTH), and amphotericin B. All diuretics can alter the normal rate and extent of secretion of anionic drugs (eg, salicylates). On a positive note, diuretics typically potentiate the BP-lowering effects of every other class of antihypertensive drug. Many combinations of a diuretic and another antihypertensive drug have been approved for marketing by the US Food and Drug Administration (FDA) and have become quite commercially successful.

Thiazide and thiazide-like diuretics can potentiate the effects of nondepolarizing muscle relaxants and antagonize norepinephrine. These effects are most commonly seen in anesthesia, rather than in outpatient hypertension clinics. Loop diuretics also antagonize tubocurarine and potentiate succinyl choline. The major loop diuretic drug interaction of concern to hospitalists is potentiation of other ototoxic drugs (eg, aminoglycosides). Eplerenone, a newer selective aldosterone antagonist, is an exception to the limited introduction of drugs that are affected by CYP3A4 inhibitors and should be used with great caution in patients who must take such drugs (eg, the *-azole* antifungal agents).

β-Blockers

All β-blockers can interfere with (and be interfered by) either digitalis preparations or NSAIDs. Like diuretics, orthostatic hypotension with β-blockers can be exacerbated by ethanol or central nervous system depressants. Catecholamine-depleting drugs and β-blockers can lead to bradycardia and heart block. The cardiac effects of nondihydropyridine calcium antagonists and lidocaine can be potentiated by β-blockers. One of the reasons that propranolol is not used nearly as widely as it once was is the vast array of drugs with which it interacts. In addition to the agents that increase its metabolism (via the CYP450 enzyme systems discussed above), the effects of propranolol are potentiated by ethanol, antithyroid drugs, haloperidol, tricyclic antidepressants, and monoamine oxidase inhibitors. Likewise, propranolol potentiates the effects of many other drugs, including amiodarone, chlorpromazine, diazepam, lidocaine, propafenone, rizatriptan, theophylline, thioridazine, warfarin, and zolmitriptan.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

These two classes of antihypertensive drugs share their propensity to be adversely affected (for BP control, fluid retention, and renal dysfunction) by NSAIDs. Both classes of drugs increase the risk of lithium toxicity and hyperkalemia, which is also seen with high-potassium foods and potassium supplements. Diuretics potentiate the BP-lowering effects of both angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). Telmisartan has an important drug interaction with digoxin that increases the latter's concentration (via an unknown mechanism).

α_1-Blockers

The major drug interaction that affects the BP-lowering effects of any α_1-blocker is with phosphodiesterase-5 inhibitors (used originally for erectile dysfunction). Although there may be less of a propensity for severe orthostatic hypotension with sildenafil, both tadalafil and vardenafil are contraindicated when an α_1-blocker is being taken for hypertension. The combination of verapamil and an α_1-blocker tends to produce more orthostatic hypotension and dizziness than either drug given alone.

α_2-Agonists

These drugs interfere with, and their effects are interfered by, both NSAIDs and monoamine oxidase inhibitors. Their effects on both orthostatic hypotension and sedation are potentiated by ethanol and other central nervous system depressants. The hypotensive effects of α_2-agonists can be antagonized by tricyclic antidepressants. Methyldopa (and possibly other less well studied

α_2-agonists) can potentiate digoxin and/or lithium toxicity and antagonize the effects of oral hypoglycemic agents.

Calcium Antagonists

Like most other antihypertensive drugs, calcium antagonists potentiate the sedation and orthostatic hypotension seen with ethanol and central nervous system depressants, are antagonized by tricyclic antidepressants, and are potentiated somewhat by diuretics. Calcium antagonists are a heterogeneous group of drugs, however, even beyond the usual dichotomization to dihydropyridine and nondihydropyridine agents. For example, many calcium antagonists (but probably not amlodipine) are potentiated by near-simultaneous consumption of grapefruit juice (probably by inhibiting prehepatic metabolism), which has therapeutic implications. Similarly, verapamil has prominent metabolism by the CYP3A4 system and is potentiated by inhibitors of this system (eg, erythromycin) and antagonized by its inducers (eg, rifampin). Cimetidine and cyclosporine have substantive interactions with most calcium antagonists; the latter's interaction with diltiazem has been used to reduce the dose of expensive cyclosporine in some centers. The potentiation of the negative chronotropic and inotropic effects of β-blockers with nondihydropyridine calcium antagonists is well known to most hypertension specialists. The use of both dihydropyridine and nondihydropyridine calcium antagonists to lower BP (especially in those with angioedema after an ACE inhibitor) is becoming more common, but a potential similarity in hepatic metabolic pathways limits the doses that do not lead to adverse effects.

ILLICIT AND UNREGULATED DRUGS THAT RAISE BP

Alterations in BP that can be attributed to illicit and nonprescription drugs and/or their interactions with antihypertensive agents are more commonly seen in the emergency department than in practitioners' offices. Nonetheless, anabolic steroids, cocaine, methylphenidate (and its congeners, including ephedra, ma huang, and other stimulants), γ-hydroxybutyrate, and even ketamine and ergotamine can be obtained; such drugs either acutely or chronically raise BP. In addition, withdrawal from heroin or nicotine acutely raises BP.

PRESCRIPTION DRUGS THAT RAISE BP

Steroids

There are 4 major types of steroids that raise BP: anabolic steroids, corticosteroids, mineralocorticoids, and estrogenic steroids. Despite the relatively weak BP-raising effects of corticosteroids (compared with mineralocorticoids), corticosteroids can cause sodium and water retention, hypokalemia, and exacerbate hypertension. Spironolactone does not prevent this glucocorticoid-associated hypertension in metabolic ward studies, however. Increased levels of renin substrate and reduced activity of various vasodepressor mechanisms have been observed in Japanese studies in which patients were given high doses of exogenous corticosteroids, after which BP became difficult to control. Some believe this is a manifestation of inhibition of 11β-hydroxysteroid dehydrogenase when cortisol or its analogs are present. Corticosteroids may be the drugs that have the highest association with hypertension, in that nearly all individuals who have cortisol excess states will develop hypertension. While there doesn't seem to be any specific antidote for corticosteroid-related hypertension, diuretics and perhaps ACE inhibitors are most commonly used.

Estrogenic steroids were formerly a major cause of hypertension, particularly when high-dose estrogen was used in oral contraceptive pills. The lower doses used today are far less likely to raise BP. Estrogenic hormone replacement therapy usually lowers BP but is seldom recommended after the Women's Health Initiative showed few benefits from it. The mechanism of estrogen-related hypertension is unclear, but it may be related to increased circulating prorenin. Most physicians who prescribe oral contraceptive pills are vigilant about monitoring BP after the first 3 months of treatment; if the BP escalates, the pills are usually stopped and the BP returns to normal.

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs are very likely the class of drug that raises BP of more people in the United States than any other class. Most people who use these drugs for arthritis or pain are old enough to be at risk for hypertension, and many take NSAIDs without informing the physician. The mechanism(s) of NSAID-related hypertension is/are unclear. Some believe the sodium part of the ion pair (eg, for naproxyn or ibuprofen) is a cause (but this would not explain the BP-raising effects of non–sodium-containing NSAIDs, such as nabumetone or celecoxib). More likely is their interference with intrarenal blood flow, which is prostaglandin-dependent. Although NSAIDs interfere with essentially all antihypertensive drugs, the rank ordering is ACE inhibitor/ARB > diuretic > β-blocker >> calcium antagonist or α-blocker.

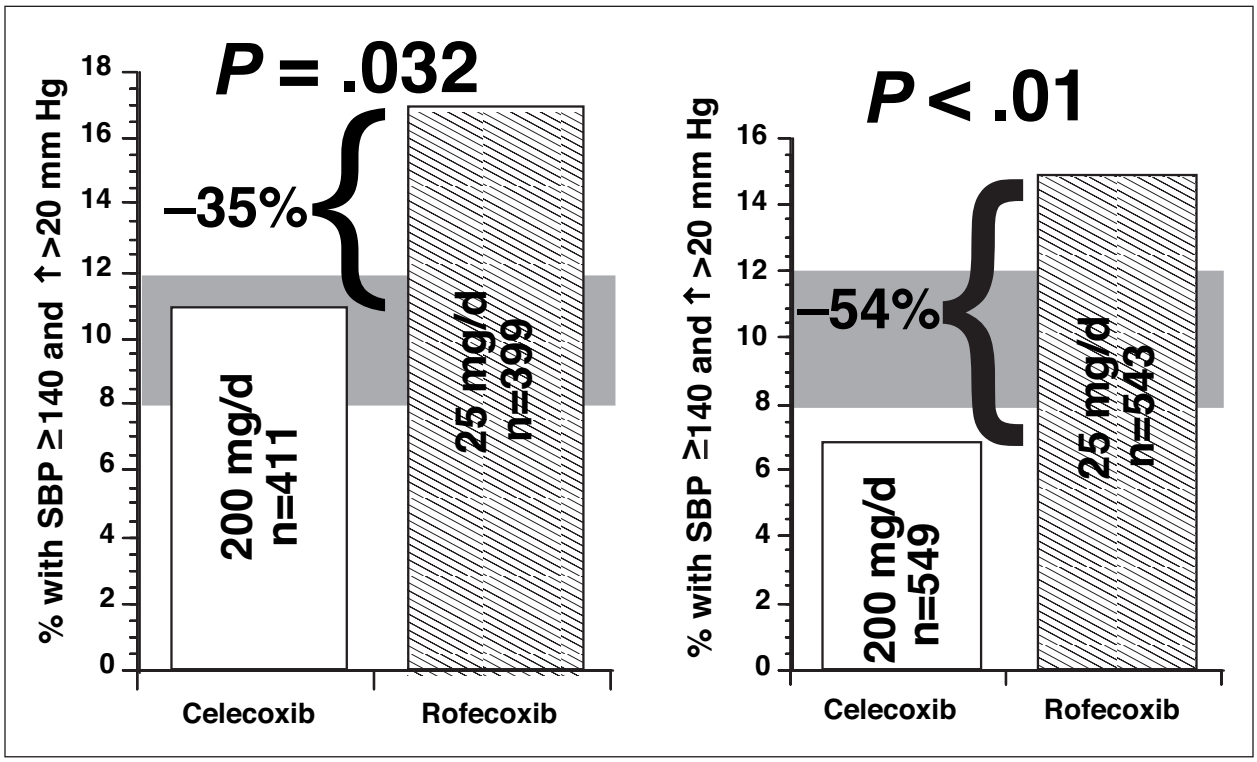

Figure 1. Results of two head-to-head randomized clinical trials designed to compare the effects of celecoxib (200 mg/d) with rofecoxib (25 mg/d) on systolic blood pressure (SBP) in 1894 treated hypertensive patients with arthritis. The primary end point for each trial was an SBP ≥140 mm Hg and an increase (↑) by 20 mm Hg compared with baseline. Both studies showed a significant difference, favoring celecoxib over 6 weeks. The dark horizontal bars between 8% and 12% represent historical ranges for this degree of BP elevation observed with nonselective nonsteroidal anti-inflammatory drugs. Data from Am J Ther. *2001;8:85–95 (left panel) and* Am J Cardiol. *2002;90:959–963 (right panel).*

Selective inhibitors of the second isoform of cyclooxygenase (COX-2 inhibitors) have now been reasonably well studied regarding their propensity to elevate BP. Generally, the few existing studies show little difference in renal dysfunction or edema incidence for COX-2 selective inhibitors compared with the traditional nonselective NSAIDs. Data from both observational studies and randomized clinical trials show some differences across the COX-2 selective inhibitors, however. Rofecoxib has essentially the same propensity to increase BP as the traditional nonselective NSAIDs, and (in data presented at the February 7, 2001, Arthritis Advisory Committee to the FDA) a dose-dependent increase in the incidence of investigator-reported hypertension was noted among the adverse experiences with rofecoxib. Neither celecoxib nor valdecoxib showed either a dose-dependent increase or an increase outside the expected range for nonselective NSAIDs. Perhaps most convincingly, two head-to-head clinical trials comparing celecoxib (200 mg/d) and rofecoxib (25 mg/d) in 1894 hypertensive patients with osteoarthritis showed a lower frequency of significant elevation of systolic blood pressure (the primary end point, defined as systolic BP ≥140 mm Hg and an increase >20 mm Hg compared with baseline) with celecoxib in both trials (Figure 1). These data have been subjected to several meta-analyses; one concluded that celecoxib had a summary odds ratio below unity, but which was not significantly better than either placebo or a nonselective NSAID in incident hypertension, whereas rofecoxib had a significantly greater risk compared with either placebo or a nonselective NSAID. Etoricoxib's risk was greater than unity, but not significantly so (Figure 2).

A presentation by Professor William B. White at the 2006 American Society of Hypertension Meeting concluded, based on 41 clinical trials involving more than 44,000 patients, that celecoxib had a somewhat higher risk of hypertension than placebo (91 of 8405 vs 27 of 4057; *P*=.023), but a significantly lower risk of hypertension than a nonselective NSAID (317 of 20,463 vs 280 of 13,990; *P*=.002; Figure 3). Professor White also put together the data from the two head-to-head clinical trials comparing celecoxib and rofecoxib on BP and showed that BP rose the most with rofecoxib in patients taking an ACE inhibitor, an ACE inhibitor + a diuretic, a β-blocker, or a β-blocker +

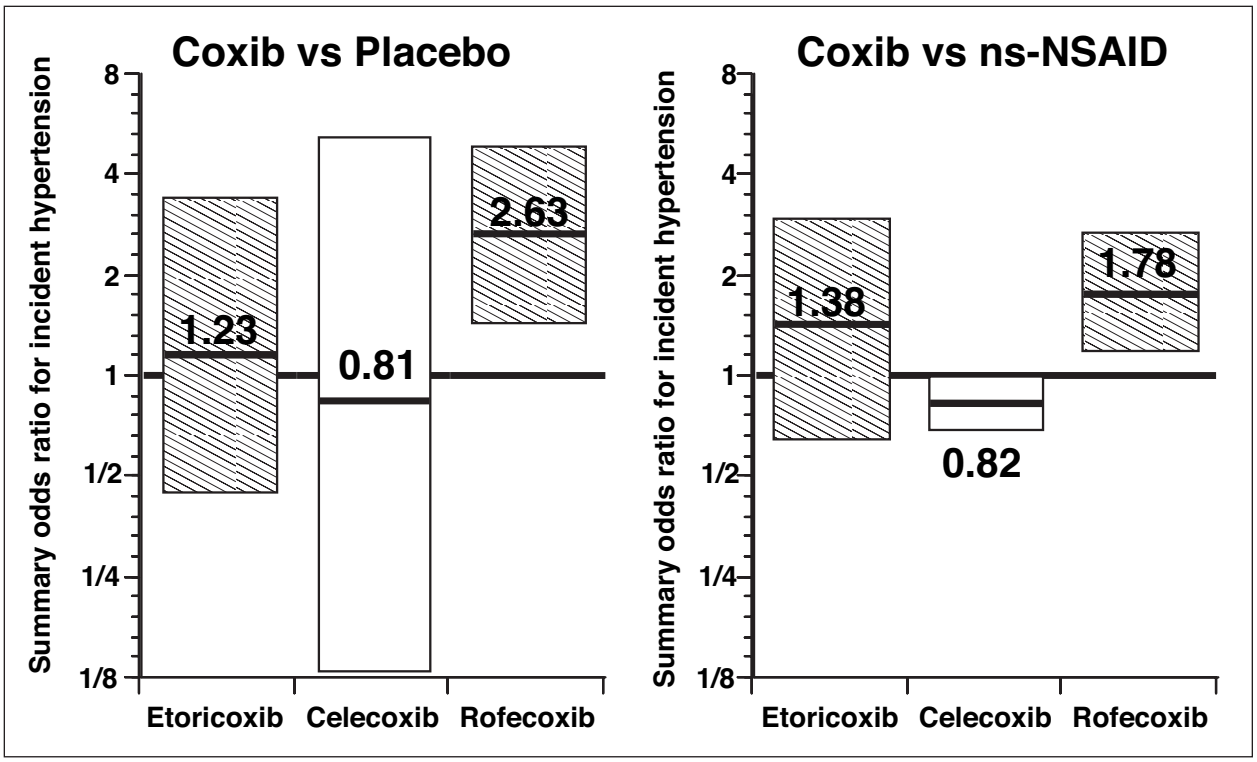

Figure 2. Results of meta-analyses of the incidence of hypertension in clinical trials comparing each of 3 selective inhibitors of the second isoform of cyclooxygenase (Coxib) with placebo (left panel) or nonselective nonsteroidal anti-inflammatory drugs (ns-NSAID, right panel). The horizontal lines inside the vertical bars represent the summary odds ratio (denoted by the number) and the 95% confidence limits, respectively. These data indicate that the largest hypertensive effect was seen with rofecoxib and that the summary odds ratio for celecoxib was less than unity, suggesting that all Coxib drugs are not alike regarding their relative propensity for hypertension. Data from Arch Intern Med. *2005;165:490–496.*

a diuretic. Those taking a calcium antagonist had a slight fall in BP with celecoxib, but a slight increase with rofecoxib, neither of which was significant. He also published the comparison of celecoxib 200 mg/d vs placebo in 178 hypertensive arthritis patients taking an ACE inhibitor, in which an ambulatory BP monitoring session showed no significant difference in 24-hour average BP between the randomized drugs. These clinical trial data have been corroborated in several observational studies, and these differences in incident hypertension (and destabilized BP) may be part of the reason that rofecoxib showed an increased risk of thrombotic cardiovascular events during long-term trials against placebo, as well as in heart failure in Ontario, myocardial infarction or sudden cardiac death in California, and myocardial infarction in New Jersey and Pennsylvania. With these exceptions, however, most of the clinical trials done with COX-2 selective inhibitors have shown benefits of the sponsor's drug, which provokes some to call for independent trials in which the maker or marketer of the drugs being studied does not directly or indirectly fund the studies.

Most authorities recommend that NSAIDs be discontinued or used only occasionally in hypertensive patients, with acetaminophen typically offered as a possible (if imperfect) substitute. Others indicate that the degree of BP elevation for most NSAIDs is only a few mm Hg, and doses of most antihypertensive drugs can easily be increased to make up for the interaction. Since exercise and especially walking are so important as lifestyle modifications to control hypertension, some patients should be allowed to take medications that make it possible for them to exercise without pain.

Phenylpropanolamines

Since at least 1970, case reports and other data indicate that most of the decongestants, cold remedies, cough suppressants, and appetite suppressants sold over the counter in the United States may raise BP, often to dangerous levels. Since 1980, these products have all carried a warning on the box to "Consult your physician before using this product if you have hypertension." On October 10, 2000, the FDA announced its intention to have products containing phenylpropanolamines removed from the market. This was supported by an important case-control study in 43

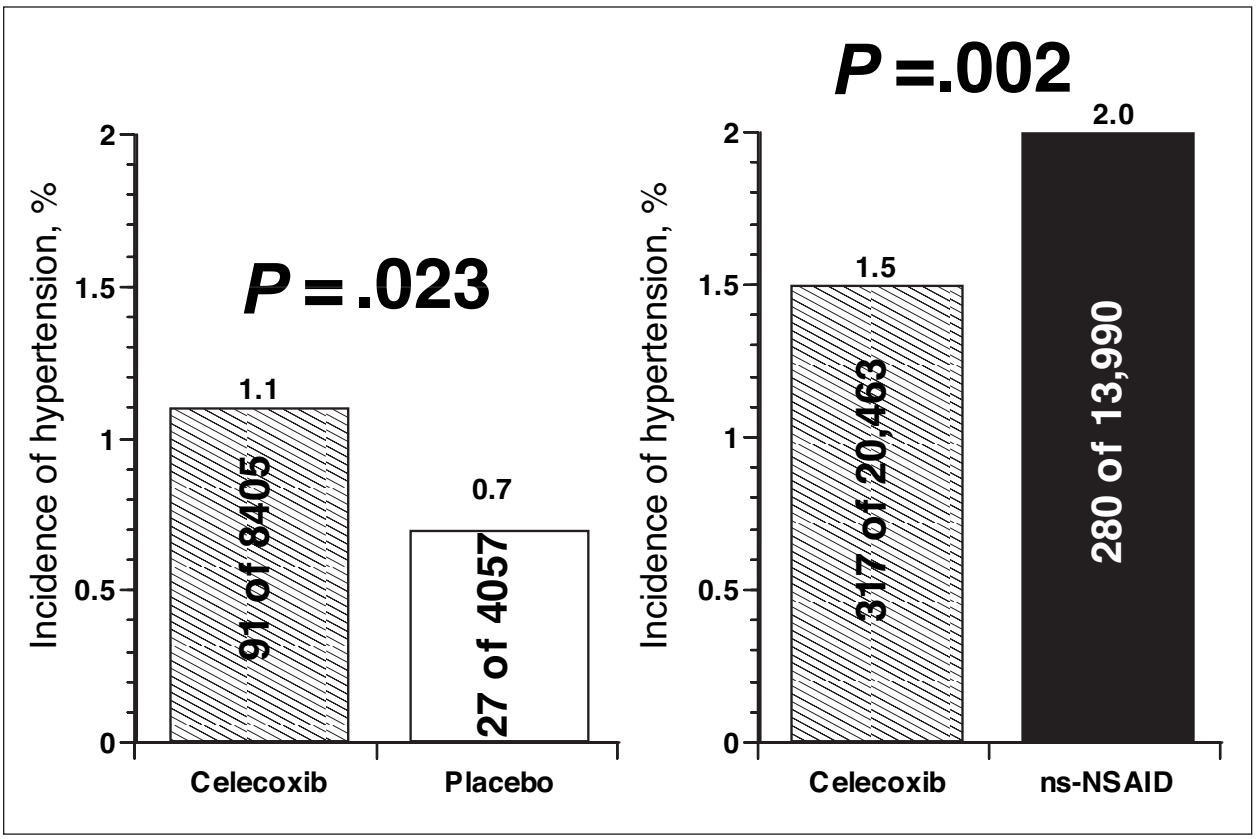

Figure 3. Results of meta-analyses of the incidence of hypertension in clinical trials comparing celecoxib with either placebo (left panel) or traditional, nonselective nonsteroidal anti-inflammatory drugs (ns-NSAIDs, right panel). The number of patients with incident hypertension and the number of patients in each treatment group are given within each bar. Data from J Clin Hypertens (Greenwich). *2006;8(5 suppl A):A245–A246.*

hospitals comparing phenylpropanolamine use in stroke patients, which showed a nearly 17-fold increase among women using these products as appetite suppressants, and a doubling of risk for all uses. The FDA issued a "Warning to Consumers" regarding these types of preparations, including those containing ephedra, which has apparently reduced the consumption of these products in the 6 years since the warning.

Sibutramine

Sibutramine is a serotonin and norepinephrine reuptake inhibitor used to enhance satiety and promote weight loss. In obese but normotensive subjects in placebo-controlled trials, it increased BP by about 3/2 mm Hg and pulse rate by 4.9 bpm; however, 5.3% became hypertensive (vs 1.4% on placebo). Recognizing that weight loss lowers BP, the manufacturer recommends monitoring BP when taking the drug, and discontinuing the drug if BP increases significantly.

Cyclosporine and Tacrolimus

Probably the most important adverse effect of cyclosporine is BP elevation, which is seen in 20%–99% of the patients receiving the drug. Alteration of the normal circadian pattern of BP is seen in essentially every patient who takes cyclosporine for a month or more. The degree of BP elevation is proportional to the dose and perhaps the duration of treatment and is seen in both solid-organ transplant recipients and those who receive the drug for other indications. Although there was initial hope that tacrolimus (also known in the older literature as FK-506) would avoid this adverse effect, at least in liver transplant recipients, there appears to be little difference between tacrolimus and cyclosporine in either hypertension incidence or nephrotoxicity.

The mechanism(s) of these effects is/are complex and may be related to binding of either drug to calcineurin, a calcium-calmodulin–dependent phosphatase. This mechanism suggests (but does not prove) that calcium antagonists might be useful in treatment, which is partly true. Most calcium antagonists have a drug–drug interaction with cyclosporine, which has led some to favor amlodipine (which has much less interaction). Others claim that diltiazem (particularly in heart transplant recipients) is preferred, since its coadministration reduces the dose and the cost of

the much more expensive cyclosporine. Clinical experience in treating calcineurin inhibitor-associated hypertension is probably most extensive at the Mayo Clinic, where isradipine and labetalol are preferentially used, but ACE inhibitors, clonidine, and other antihypertensive drugs have occasionally been useful (and necessary). In 1994, an international clinical trial was proposed, randomizing transplant recipients to either a calcium antagonist or an ACE inhibitor as initial therapy, but most transplantation surgeons refused to enter their patients because their protocols were already established.

Erythropoietin

The major adverse effect of recombinant human erythropoietin (rh-EPO) is hypertension, which usually appears 2–16 weeks after starting the drug, concomitantly with the increase in hematocrit level. The most extensive experience with this is in dialysis patients, in which the insidious onset of an increase in BP was often ignored in years past; now more attention is being paid to this as a quality-of-care indicator. Most patients whose BP increases with rh-EPO are easily treated with a slight increase in the dose of one of their established antihypertensive drugs; in one series, 42% of patients were successfully controlled with antihypertensive monotherapy. Based on theory (and little evidence), calcium antagonists and/or α-blockers have been recommended, since diuretics, ACE inhibitors, and ARBs should be somewhat less effective. Similar to the situation with calcineurin inhibitors, the hypertension that results from rh-EPO therapy is typically treated with more antihypertensive drugs, rather than attempting to reduce or eliminate the proximal cause of the BP elevation.

CONCLUSIONS

All the major classes of antihypertensive drugs have important interactions with other drugs, but these are seldom important (as a cause of BP elevation) with recently approved antihypertensive drugs. This is a good example of selection bias, because agents that lower BP but have significant drug–drug interactions are seldom developed past phase 2 clinical testing. The two classes of drugs that raise BP most often in Americans are NSAIDs (including COX-2 selective inhibitors) and steroids, both of which are recommended to be used sparingly whenever possible. This recommendation is often difficult to implement. Lastly, calcineurin inhibitors and rh-EPO raise BP in most patients, but because they are medically necessary for most patients who receive them, BP treatment is usually intensified, rather than discontinuing or reducing the doses of these two drugs.

Disclosure: Presented in part at the Twenty-First Scientific Meeting of the American Society of Hypertension in New York City, on May 18, 2006.

SUGGESTED READING

- Maas R, Boger RH. Antihypertensive therapy: special focus on drug interactions. *Expert Opin Drug Saf*. 2003;2:549–579.
- Carter BL. Antihypertensive drug interactions. *Drugs Today (Barc)*. 2005;41:55–63.
- Grossman E, Messerli FH. High blood pressure: a side-effect of drugs, poisons, and food. *Arch Intern Med*. 1995;155:450–460.
- Vora CK, Mansoor GA. Herbs and alternative therapies: relevance to hypertension and cardiovascular diseases. *Curr Hypertens Rep*. 2005;7:275–280.
- Draper N, Stewart PM. 11β-Hydroxysteroid dehydrogenase and the pre-receptor regulation of corticosteroid hormone action. *J Endocrinol*. 2005;186:251–271.
- White WB, Kent J, Taylor A, et al. Effects of celecoxib on ambulatory blood pressure in hypertensive patients on ACE inhibitors. *Hypertension*. 2002;39:929–934.
- White WB, Simon LS, MacDonald TM, et al. Effects of celecoxib on cardiorenal adverse events: meta-analysis of 41 clinical trials in over 44,000 patients [abstract]. *J Clin Hypertens (Greenwich)*. 2006;8(5 suppl A):A245–A246. P-602, MP-54.
- Aw T-J, Haas SJ, Liew D, et al. Meta-analysis of cyclooxygenase-2 inhibitors and their effects on blood pressure. *Arch Intern Med*. 2005;165:490–496.
- Whelton A, Fort JG, Puma JA, et al, for the SUCCESS VI Study Group. Cyclooxygenase-2-specific inhibitors and cardiorenal function: a randomized controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients [published correction appears in *Am J Ther.* 2001;8:220]. *Am J Ther.* 2001;8:85–95.
- Whelton A, White WB, Bello AE, et al, for the SUCCESS VII Investigators. Effects of celecoxib and rofecoxib on blood pressure and edema in patients > or =65 years of age with systemic hypertension and osteoarthritis. *Am J Cardiol.* 2002;90:959–963.
- Jordan J, Scholze J, Matiba B, et al. Influence of sibutramine on blood pressure: evidence from placebo-controlled trials. *Int J Obes (Lond)*. 2005;29:509–519.
- Taler SJ, Textor SC, Canzanello VJ, et al. Cyclosporine-induced hypertension: incidence, pathogenesis and management. *Drug Saf*. 1999;20:437–449.
- Luft FC. Erythropoietin and arterial hypertension. *Clin Nephrol*. 2000;53(suppl 1):S61–S64.