The use of alternative therapies, herbs, and supplements occurs at a very high rate among patients attending a variety of health care settings. Such therapy may cause significant interactions or effects on hypertension and other cardiovascular disorders and needs to be considered by clinicians. In this brief review, we highlight several commonly used alternative therapies that may have a clinical impact in the hypertensive patient. Several problems hinder our complete awareness of these effects. These problems include patients not informing physicians about alternative treatment or herbal use, the lack of consistent scientific standards for the bioactivity of many herbals or supplements, and the multiple names that each bioactive substance is sold under. Specific questioning regarding herbals and alternative therapies in the hypertension clinic is therefore needed. Herbals including ma huang, St. John’s wort, yohimbine, garlic, and licorice all may cause important consequences in the hypertensive patient. Added care is needed in monitoring the use and effects of herbal and alternative therapies in the hypertensive population. Am J Hypertens 2001;14:971–975 © 2001 American Journal of Hypertension, Ltd.

Key Words: Hypertension, alternative medicines, ephedra, licorice, St. John’s wort.

The large number of patients taking herbals or alternative therapies suggests a likelihood that interactions of these agents with cardiovascular drugs will occur. The usage of herbal and nutritional supplements is widespread in the United States with up to 90% of patients taking either over-the-counter medications or supplements depending on the definitions used. In a recent survey performed in a primary care setting in Alabama, 41% of patients were taking nutritional supplements and 26% were taking herbal products. The combined rate of herbal and supplement use and home remedies (excluding calcium and vitamin supplements) was 48%. Consistent with other studies, persons with a higher income and more education were more likely to be takers of herbal products. Studies in other patient populations have also shown a significant prevalence of supplement, herb, and other alternative therapy use. It is, therefore, commonplace for patients attending a medical care setting to use supplements or herbs. Unfortunately, most patients do not reveal the use of such treatments to their health care providers. Although there are no data on the prevalence of use in hypertension clinic populations, it is likely that such treatments are also widely used in this population. Therefore, it is important for the physician treating hypertension and its comorbidities to be aware of the possibility that patients are taking such therapies and consider their possible effects on therapeutic goals and drug–herb interactions. Clinicians should have a comprehensive source of information detailing herbals, supplements and their potential uses, side effects and interactions.

Patients with cardiovascular disease including hypertension deserve special attention with regard to this issue. Hypertension is very prevalent with some 50 million Americans diagnosed with hypertension and the majority is taking antihypertensive drugs. Furthermore, there are now at least six classes of antihypertensive drugs with their unique mechanisms of action and potential for interactions with supplement and herbal use. Also, because of the fact that tighter goals for the treatment of hypertension, hyperlipidemia, and hyperglycemia have been recommended, multidrug therapy is routine for these disorders. In the case of hypertension, the achievement of goal blood pressure (BP) especially in high-risk patients with diabetes or renal disease routinely requires multiple drugs. Therefore, not only is it likely that drug–drug interactions will occur as the number of drugs increases in an individual patient but also the likelihood that drug–supplement or drug–herb interactions will occur.

Traditional drug–drug interactions have been described based on drug absorption, metabolism, elimination, and on the pharmacodynamic effects and many of these mecha-
nisms have been identified and studied. The pharmacokinetic drug interactions are easier to predict and explain, but multiple factors affect pharmacodynamic interactions. It is likely also that interactions of herbs and supplements with these agents will also affect the pharmacokinetic or pharmacodynamic properties of antihypertensive drugs.

This brief review focuses on known and potential herb–drug interactions of relevance to the physician treating hypertension. Although the focus is on agents affecting the treatment of hypertension, reference will be made to other cardiovascular drugs that are commonly taken by hypertensive patients. The content is not meant to be exhaustive but to be illustrative and to sharpen awareness of these possible interactions.

Lack of Regulation of Dietary and Herbal Supplements

Dietary supplements including vitamins, amino acids, botanicals, and other substances such as pyruvate and steroid precursors are regulated as foods. This stems directly from the Dietary Supplement Health and Education Act that does not require governmental oversight of these products and relies on self-regulation. Only when a specific disease treatment claim is made, Food and Drug Administration approval is needed. Therefore, manufacturers are mainly responsible for safety and accuracy of the labeling of such products. Where there has been a pattern of human use of a substance, safety has been essentially assumed and no studies before marketing are needed. This has led to de facto self-regulation in the industry.

The industry continues to grow at an amazing pace and sales were estimated in 1999 at some 10 billion dollars. The largest chunk of this expenditure is for vitamins (48%), and herbs and botanicals (28%). Among herbs, garlic and ginseng each account for about 29% of the market share with gingko biloba taking 14%.

Difficulties With Product Identification

There are some very basic problems with some herbals and supplements. The active product of a particular herb may not be known or if known may not be on the label. Furthermore, the amount of the active substance stated may not be accurate. Quality control measures vary from company to company and from product to product.

For example, Gurley and colleagues compared ephedra amounts on the product label to actual assayed amounts in 20 ephedra-containing supplements. Ephedra contains several alkaloids including ephedrine, pseudoephedrine, methyl-ephedrine, nor-pseudoephedrine, and norephedrine. These substances are sympathomimetic agents with an amphetamine-like action with varying potencies and are marketed as energy enhancers and weight loss products. Depending on the manufacturer, the label may indicate either individual amounts of the various alkaloids or total amounts, or both. After careful quantitative analysis of the various alkaloids, these researchers found considerable variability in the content of ephedra. The amounts of ephedrine varied from 1.09 mg per capsule to 15.33 mg per capsule and pseudoephedrine varied from 0.16 mg per capsule to 9.45 mg per capsule. Lot-to-lot variability was seen in several samples with some being as high as 1000%. No correlation was found between the claimed amount of ephedra and the actual amounts found by analysis. These results and other findings show that there is suboptimal quality control and consistency with some products. In addition, these products may contain multiple ephedra alkaloids that may cause summation adverse effects by acting through similar mechanisms of action. The authors of this article also point out that the Food and Drug administration has not approved any product with multiple ephedra-like alkaloids because of fear of synergistic side effects. In addition, many herbals also contain caffeine that may increase the toxicity of ephedra alkaloids. Consumers should consider buying from manufacturers that have obtained Pharmacopeia standards for product purity and content reliability, thus at least ensuring some standards are used in manufacture.

Patient Interview

Because many patients do not consider supplements, herbs, or alternative treatments as relevant to medical practice, they may either intentionally or unintentionally not tell the physician about their use. For example, in a recent survey completed in an emergency room in a suburban area of New York, 24% of a consecutive sample of 139 patients reported using herbs. Most of the patients who had taken alternative therapies did not inform their physicians about such use. Similarly, among 755 patients undergoing preanesthetic evaluation, about one third were self-administering one or more herbs or related compounds and 70% of these patients did not report this information on their medical assessment. This makes it very important to ask patients specifically about alternative medicine use in a nonjudgmental way and after establishing patient confidence. Inquiry should not only include items bought over the counter but also items from another country or bought over the internet or through mail order. An appreciation of the cultural background and beliefs of the patient regarding herbal dietary supplements may help in establishing trust with the patient. Such history taking is also important in the hypertension clinic.

Specific Herbs or Supplements

Ephedra or Ma Huang

This is one of the most commonly taken supplements and is called by a variety of names including ma huang,
Caffeine extract, ephedra sinica, ephedra equisetina, ephedra intermedia, ephedra geradiana, ephedra herb powder, epitoxin, or ephedrine. All these names indicate the presence of ephedrine. Ephedra is sold as treatment for asthma, cold and flu symptoms, and weight loss. Combinations of other herbs and ephedra are also sold. For example, herbal phen-fen is marketed as a weight loss supplement and contains St. John’s wort along with ma huang. It is very common for caffeine to also be present in these supplements along with ephedra. Ephedrine stimulates adrenergic receptors and can increase heart rate and peripheral vascular resistance. It can also act on the central nervous system giving the individual a feeling of tremendous well-being.

There is due cause for concern about ingestion of ephedra-containing supplements in persons with hypertension and heart disease. In a recent report, Haller and Benowitz independently reviewed 140 adverse events related to dietary supplements containing ephedra. These represented reported cases between June 1, 1997 and March 31, 1999, in the FDA Medwatch report. The reports involved persons of all age groups including children. Thirty-one percent were believed by the independent reviewers to be definitely or probably related to ephedra use, with another 31% possibly related to ephedra use. In 17%, the reviewers believed that the event was unrelated to ephedra use and another 21% no opinion could be rendered due to lack of clinical information. Most of the events considered possibly, probably, or definitely related to ephedra use were cardiovascular in nature. Hypertension, tachycardia, or palpitations were the most common adverse effect in 30% and cardiac arrest in 8% of the total reports. Strokes also occurred in 10% and seizures in 7% of all the reports. In 26% of patients, these adverse events resulted in death or permanent disability. Similarly, in a 2-year period in Texas, some 5000 reports of adverse effects of dietary supplements containing ephedra were reported.

It makes good sense to specifically instruct patients with hypertension, diabetes mellitus, thyroid disease, cardiac rhythm disorders, and seizures not to take herbal supplements with ephedra. Drug interactions expected for ephedrine are also likely with ma huang. In normotensive subjects, the effects of ma huang on BP and heart rate appear unpredictable, but it undoubtedly can precipitate a hypertensive crisis in certain individuals when combined with caffeine.

An additional cause of concern for clinicians treating hypertension is the reported association of kidney stones with ephedra ingestion. Chemical analysis has revealed these concretions to contain ephedrine and its metabolites. Renal calculi containing ephedrine have also been found in patients consuming large amounts of guaifenesin and ephedrine in over-the-counter preparations. It should be noted that ephedra has also been linked to cases of psychoses, mood disorders, and myocarditis.

St. John’s Wort

This is a derivative of the plant Hypericum perforatum used for the treatment of mild depression. It can be obtained as a tea, capsule, or oil. St. John’s wort contains several active ingredients that have a variety of effects on neurochemical signals in the central nervous system. It has undergone significant scientific testing including double blind clinical trials and is widely used in Germany. In a meta-analysis of 23 randomized trials with St. John’s wort, it appears to show similar response rates in the treatment of depression as tricyclic antidepressants and was also better tolerated.

The main concern regarding St. John’s wort of particular interest to the hypertension physician is the reported interaction with several medications including cyclosporin, protease inhibitors, and some cardiovascular drugs. St. John’s wort has been shown to induce both liver and intestinal CYP3A. This may have clinical consequences and in a recent report, two patients experienced acute rejection of a heart transplant suggested to be due to lowering of cyclosporin levels in patients taking St. John’s wort. Other expected interactions based on the CYP3A induction would include with digoxin and possibly calcium channel blockers. Close monitoring is appropriate if St. John’s wort is taken with substrates of the CYP3A system.

Garlic

Garlic is commonly used among hypertensive patients because of its reputed benefit in reducing cardiovascular disease and lowering BP. Other claims for the benefits of garlic have included cancer prevention and anti-inflammation. Studies have suggested a multitude of physiologic effects including inhibition of platelet activity and increased levels of antioxidant enzymes. There are probably several active ingredients in garlic preparations.

Not surprisingly, several studies have been done to examine its utility in treating hypertension and hyperlipidemia. In its evidence report, on garlic, the Agency for Health Care Research and Quality reviewed 37 randomized trials and found that garlic preparations did indeed lower total cholesterol by small amounts in the short term but no reduction was observed at 6 months. In the treatment of high BP, 27 small randomized placebo controlled trials of short duration were reviewed. Various doses of garlic were used providing about 3 to 6 mg of allicin per day. The majority of these studies found that garlic did not reduce BP compared to placebo, but the studies were small. Interestingly, in one cross-sectional observation study of older patients, garlic intake was found to reduce age-related increases in aortic stiffness. Garlic has been reported to increase the risk of bleeding, probably due to its antiplatelet action, but this is not well studied.
Yohimbine

This is a prescription drug that has been available for about 30 years and has long been known to be present in the bark of a West African tree. The bark product contains several alkaloids including yohimbine that may be present in varying amounts. Yohimbine is a presynaptic α₂-adrenergic blocking agent and possibly a monoamine oxidase inhibitor. It also has other effects on the autonomic nervous system. Although not available as an over-the-counter product, it can be found in herbal and supplement stores and is promoted as treatment for erectile dysfunction.

It has been fairly well documented that yohimbine can increase BP in humans and should be used with caution if at all in hypertensive patients. The pressor effect of yohimbine is seen at low (10 mg) and higher doses (22 mg). One case report implicates yohimbine as the cause of a hypertensive emergency in a 63-year-old man taking yohimbine for erectile dysfunction. Of additional concern is the increase seen in norepinephrine with yohimbine use, a particular concern for patients with coronary artery disease or congestive heart failure. The drug should also not be used in patients taking tricyclic antidepressants.

Licorice

Of course, physicians treating hypertension in the United States should be aware of licorice. It is marketed for the treatment of stomach disorders and is associated with a form of pseudohypertension manifesting as weight gain, hypertension, hypokalemia, and metabolic alkalosis. The implicated substance is glycyrrhizic acid that inhibits 11-β-hydroxysteroid dehydrogenase and hence increased levels of cortisol that combine with the mineralocorticoid receptor (an acquired apparent mineralocorticoid excess). The disorder reverses within a few days on cessation of intake of licorice but may be associated with hypertensive encephalopathy and chronic refractory hypertension.

Interactions With Drugs and Drug Metabolism

Many herbs can increase digoxin levels or potentiate the effects of digitalis. This is because many herbs contain digitalis-like glycosides. Many herbs and supplements can also affect anticoagulation levels or bleeding times. Especially in the case of coumadin that has a narrow therapeutic range, such interactions may be serious. Indeed several case reports attest to this in patients taking certain supplements. Some drugs that may increase warfarin anticoagulation include vitamin E, dan-shen, dong quai, and devil’s claw, whereas ginseng and coenzyme Q may reduce its effect.

Grapefruit juice, although not an herbal in the way it is used in this article, is also of concern to the hypertension physician because of its effect on the metabolism of many cardiovascular drugs. By inhibiting intestinal CYP3A, it can increase the bioavailability of many substrates of CYP3A, including immunosuppressive drugs, certain HMG-Co-A reductase inhibitors, and most dihydropyridine calcium channel blockers. The effect is robust and quick in onset and lasts for up to 24 h after ingestion of the juice. One glass of 200 mL of juice can significantly inhibit intestinal CYP3A. The chemical content of grapefruit that causes this effect has been suggested to be flavonoids and nonflavonoids, although this is by no means certain. The effect of grapefruit juice was first discovered with felodipine and other 1,4 dihydropyridine calcium antagonists are also targets for this interaction. The effect is much less pronounced in the highly bioavailable drugs amlodipine and nifedipine. There is conflicting data regarding the non-dihydropyridine drugs, verapamil and diltiazem.

A more serious problem was reported in which a manufacturing error resulted in a nephrotoxic and carcinogenic herb (Aristolochia fangchi) being ingested by patients who later developed interstitial fibrosis and rapid progression to end-stage renal failure. These patients were generally women who took these herbs to lose weight and some had prolonged intake. Unfortunately, a substantial number of these patients developed urothelial carcinomas. This illustrates the serious and widespread problems that may arise in the manufacture, distribution, and toxicities of herbal preparations.

Conclusions

It is essential for all physicians treating hypertension to obtain a history of any herbal, dietary, or supplement use from all patients. Because of the potency of the effect of grapefruit juice on several drugs used in hypertensive patients, specific questioning is needed about this. The number and complexities of such substances and their possible interactions with cardiovascular drugs make it imperative that a written or electronic reference source be immediately available for consultation. Serious consideration should be given to having all patients attending a hypertension clinic discuss use of any such products with their physician before intake. Case reports and case series of hypertensive emergencies and serious cardiovascular complications illustrate the serious adverse effects that may occur. More vigilance is needed in monitoring the use of herbs, supplements, and other nontraditional medications in the hypertensive population.

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