Evolving concepts and a new approach for management of hyperlipidemia

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Although treatment of modifiable risk factors for coronary heart disease (CHD), including hypertension and hyperlipidemia, constitutes a large proportion of visits to family practitioners, most surveys reveal that neither hypertension nor hyperlipidemia are treated to targets specified by national guidelines. Current recommendations for the management of hypertension have evolved from earlier recommendations to titrate to high-dose monotherapy if needed to an emphasis on combination therapy, which can achieve greater efficacy than monotherapy without the increased side effects associated with a high-dose single agent.


Key Words: Cholesterol-lowering drugs, combination therapy, ezetimibe, hyperlipidemia, treatment.

Introduction

Drug treatment for hypertension has a longer history than does pharmacotherapy for hypercholesterolemia, and lessons can be learned from the evolution of management of hypertension (Fig. 1). When the guidelines of the first Report of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure (JNC I) were published in 1977, treatment with a diuretic with titration to a high dose as needed to achieve target blood pressure was recommended as initial therapy for patients who needed drug therapy[1]. Recommendations for use of alternative drugs, including β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and calcium-channel blockers, were added over the next several editions of the guidelines[2–4]. High doses of single agents were still recommended therapy in JNC V, published in 1993[5]. However, with the publication of JNC VI in 1997[6], low-dose combination therapy was recognized as a secondary option. JNC VII is expected to emphasize combination therapy as a primary choice in hypertension control. The importance of combination therapy for the treatment of hypertension is reflected in the availability of more than 20 commonly prescribed agents that contain two drugs in a single pill.

The recognition of the importance of combination therapy for hypertension has been fueled by several factors. The JNC VI guidelines[6] recommend target blood pressures considerably lower than the previous JNC V recommendations, thus necessitating more aggressive intervention to reach target goals. Titration of a single agent to a very high dose begins to have an unfavorable profile in regard to benefits and adverse effects. At high doses, the beneficial effects begin to ‘flatten out’, whereas the side effects may increase exponentially (Fig. 2)[7]. For example, if one quadruples the dose of hydrochlorothiazide from 25 mg once daily to 50 mg twice daily, there is only a modest benefit on further blood pressure reduction but there is a dramatic increase in incidence of adverse effects such as hypokalemia and hypomagnesemia. Clinicians realized that addition of a low dose of two agents, such as a diuretic and an ACE inhibitor, could provide additive efficacy without adding adverse effects. This has provided the rationale for an increasing number of antihypertensive agents that provide two different drugs in a single pill.

Guidelines for the management of hyperlipidemia

Recommendations for the management of hyperlipidemia have evolved in parallel with those for hypertension (Fig. 3). In the first National Cholesterol Education Program Adult Treatment Program Guidelines (ATP I)[8],
patients were divided into two risk categories that determined the level of low-density lipoprotein cholesterol (LDL-C) at which therapy should be initiated and the goal of therapy: high-risk patients, defined as patients with CHD or with two CHD risk factors, and patients with less than two CHD risk factors. LDL-C goals for these respective groups were <130 mg/dl and <160 mg/dl. Niacin and resins were considered drugs of first choice, whereas statins were classified as new drugs, without long-term safety information and so requiring caution; fibrates were included with other drugs[8]. With the publication of ATP II[9], CHD risk stratification was refined to three categories: patients with CHD, patients without CHD who have two or more risk factors, and patients without CHD who have less than two risk factors. The LDL-C target for patients with CHD became more stringent (≤100 mg/dl), and statins were now classified as major drugs, along with resins and niacin, and fibrates were included with other agents[9]. ATP III[10], published in 2001, includes in the highest-risk category not only patients with CHD but also patients with CHD risk equivalents, defined as other atherosclerotic disease, diabetes, and a calculated 10-year risk for CHD >20%. Patients without CHD who have two or more risk factors are dichotomized by calculated 10-year risk of 10–20% or <10%, and the lowest-risk category remains patients without CHD who have less than two risk factors. With these changes in risk stratification, more patients have an LDL-C goal of <100 mg/dl, and more patients without CHD who have milder LDL-C elevations (130–160 mg/dl) will need therapy because of high global risk. Under the new guidelines, it is estimated that the number of Americans requiring lipid-lowering drug therapy will increase to 36 million. Statins are now recognized as first-line drug therapy. Results of the Heart Protection Study[11] and ongoing clinical trials may lead to modification of U.S. as well as European guidelines, toward even more aggressive LDL-C lowering than suggested in current guidelines.

Combination therapy with ezetimibe

The evolution of hypertension management may provide lessons for the treatment of dyslipidemia. In current clinical practice, hyperlipidemia is generally managed with monotherapy. Although therapy with statins and other lipid-modulating agents is effective in reducing the morbidity and mortality associated with CHD, the number of patients who attain treatment goals is suboptimal. Combination therapy may allow additional patients to achieve recommended goals. Current combinations provide added efficacy but also increased side effects that may be unacceptable. The cholesterol absorption inhibitor ezetimibe is the first new class of drugs since the development of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor lovastatin. The mechanism of action, pharmacology, and pre-clinical data are reviewed by van Heek and Davis. The available clinical trial data on ezetimibe as monotherapy, in combination with statins, in combination with fenofibrate, and in special patient populations are reviewed in the next article. Finally, the role of ezetimibe in combination therapy in clinical practice is reviewed by Dr. Neil Stone. In summary, the authors hope that this supplement provides useful information to physicians and other health care providers to determine how ezetimibe may be used to help manage patients with hyperlipidemia.
References


