SEMINARS IN
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Clinical Pharmacology of Antihypertensive Therapy

Addison A. Taylor and James L. Pool

Adequate control of blood pressure poses challenges for hypertensive patients and their physicians. Success rates of greater than 80% in reducing blood pressure to target values among high-risk hypertensive patients reported by several recent clinical trials argue that effective medications currently are available. Yet, only 34% of hypertensive patients in the United States are at their goal blood pressure according to the most recent national survey. Rational selection of antihypertensive drugs that target both the patient's blood pressure and comorbid conditions coupled with more frequent use of low-dose drug combinations that have additive efficacy and low adverse-effect profiles could improve significantly US blood pressure control rates and have a positive impact on hypertension-related cardiovascular and renal mortality and morbidity. This article reviews the pharmacokinetic and pharmacodynamic principles that underlie the actions of drugs in each of the classes of antihypertensive agents when used alone and in combination, provides practical pharmacologic information about the drugs most frequently prescribed for treatment of hypertension in the outpatient setting, and summarizes the current data influencing the selection of drugs that might be used most effectively in combination for the majority of hypertensive patients whose blood pressures are not controlled adequately by single-drug therapy.

KEYWORDS antihypertensive drugs, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel antagonists, beta blockers, diuretics, alpha-1 adrenergic blockers, combination therapy

Uncontrolled hypertension is the most common treatable cause of cardiovascular and renal morbidity and mortality. There currently are more than 200 different drugs approved by the US Food and Drug Administration that are available to physicians in the United States to treat hypertensive patients. Despite the introduction of newer drugs that not only reduce cardiovascular mortality and morbidity but do so with fewer adverse effects than older antihypertensive agents, blood pressure is controlled to levels currently recommended by the most recent national guidelines in only one third of patients with hypertension.[1]

Numerous clinical trials have documented that 2 or more drugs are needed to control blood pressure in a majority of patients. One additional lesson learned from the Antihypertensive Lipid Lowering Heart Attack Trial[2] (ALLHAT) was that even though blood pressure may be controlled initially on a single antihypertensive medication, additional medications may need to be added over time to maintain goal blood pressure values.[3] In the ALLHAT trial about 70% of patients had achieved goal blood pressure values 6 months after randomization to single-drug therapy. After 5 years of follow-up evaluation, however, only about 30% of patients remained controlled on monotherapy and 70% required 2 or more drugs. Physicians often are reluctant to add medications to a patient's therapeutic regimen for a variety of reasons. In addition, a large minority of patients do not take their medications as prescribed because of cost, adverse effects, social stigmata, or other reasons. Thus, primary care physicians and specialists alike must be familiar with both the actions and the adverse effects of antihypertensive drug classes so they can treat patients with the most therapeutically and cost-effective drugs or drug combinations while minimizing adverse effects that may precipitate discontinuation of therapy by the patient. This article reviews the pharmacologic actions and adverse effects of the most commonly prescribed drugs for the treatment of hypertension in the outpatient setting. A working knowledge of this information allows clinicians to make rational choices of drugs or drug combinations both for treatment of the uncomplicated hypertensive patient and for subgroups of the hypertensive population who pose unique challenges such as African Americans, the elderly, diabetics,

From the Section on Hypertension and Clinical Pharmacology, Department of Medicine, Baylor College of Medicine, Houston, TX.
Address reprint requests to Addison A. Taylor, MD, PhD, Section on Hypertension and Clinical Pharmacology, Department of Medicine, Baylor College of Medicine, Houston, TX 77030. E-mail: ataylor@bcm.tmc.edu.

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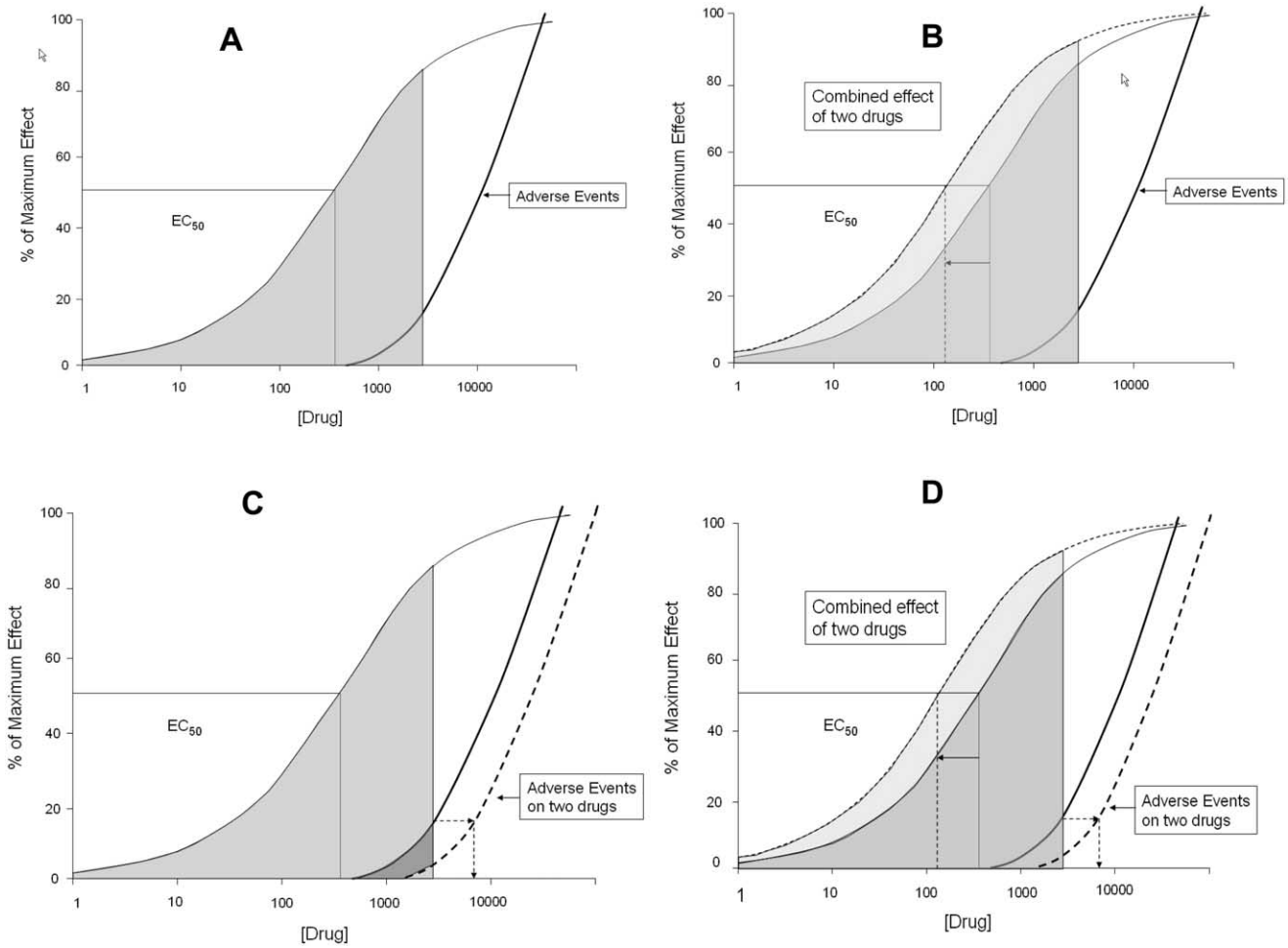

Figure 1 Panel A depicts a typical sigmoid dose-response relationship between [Drug] concentration on the x-axis and the % of maximum drug effect on the y-axis. The dose of drug which elicits 50% of the maximum effect (EC_{50}) is illustrated by the horizontal line. Adverse events (solid black line) typically are either absent or of low incidence until the drug dose is increased to well above the EC_{50}. For this reason, it is preferable to avoid using doses of drug which are near the maximum effect.

Panel B illustrates the effect on the EC_{50} when a second drug is added to the first (light and dark gray areas). The effectiveness of the drug combination compared to that of a single drug (dark gray) is increased by using low doses of two drugs with little effect on the incidence of adverse events.

Panel C illustrates an effect of reducing the dose-dependent incidence of adverse events attributable to the first drug by adding a second drug which reduces the adverse events caused by the first drug.

Panel D illustrates the effect of using two drugs that, when combined, have not only greater efficacy but also a reduced incidence of adverse events.

and patients who already have experienced a stroke, myocardial infarction, renal damage, or congestive heart failure.

General Principles of Antihypertensive Drug Therapy

Many antihypertensive drugs exhibit a dose-response relationship similar to that shown in Figure 1A. One characteristic of this relationship is a threshold dose below which there is no discernible effect of the drug. When a change in systolic or diastolic blood pressure is the measured response, the Food and Drug Administration usually has required that the manufacturer define the lowest effective dose of the drug under consideration and this information is included in the drug's product monograph. Once the dose is higher than this threshold there usually is a relatively steep increase in the response when plotted against the logarithm of the dose until further dosage increases produce no additional response. The dose that produces a concentration of the drug which exerts 50% of the maximum effect is the EC_{50}. The EC_{50} is the dose that produces 50% of the maximum effect. The characteristics of the dose-response relationship for a particular drug are defined not only by the dose of the drug but by the response against which it is plotted. For example, the maximum antihypertensive effect of an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin-receptor blocker (ARB) may be achieved at a dose that does not maximize the effect of these drugs on proteinuria.[4,5] In fact, a compelling argument