

COMMENTARY

Current Use of Diuretics in the Management of Hypertension

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INTRODUCTION

No single class of antihypertensive drugs has had as much impact on the treatment of hypertension as diuretics. The introduction in the late 1950s of chlorothiazide and its analogues revolutionized the treatment of hypertension. Working then as a research fellow in hypertension with Dr Robert Wilkins at Boston University, I observed firsthand the effects of this new therapy that dramatically changed our ability to control hypertension. The availability of these effective and well-tolerated drugs led to placebo-controlled trials, such as the Veterans Administration Cooperative Trials and the Systolic Hypertension in the Elderly Program (SHEP) study, which demonstrated the benefits of blood pressure lowering in individuals with severe and mild forms of hypertension and those with isolated systolic hypertension. Despite the passage of almost 60 years, diuretics have remained important in managing hypertension when used either alone or in combination with other antihypertensive agents.

A controversy has developed in the past few years as to whether the effects of thiazides and thiazide-type diuretics as chlorthalidone and indapamide are alike in the management of hypertension. In this edition of the *Hypertension Journal*, Dr Anil Pareek and his associates have addressed the issue and have provided a comprehensive review that includes their own recent clinical data to support the preferential use of chlorthalidone rather than hydrochlorothiazide in hypertension. Despite its early approval for the treatment of hypertension, which came soon after that of hydrochlorothiazide,

chlorthalidone has had relatively minimal use since then, probably because of its early reputation of causing more hypokalemia and other metabolic abnormalities than the thiazides. However, in retrospect, such a reputation was garnered because of the high doses of chlorthalidone used initially which averaged more than 50 mg per day, or more than eight times that employed in the studies of Pareek and associates. Clinicians have continued to shy away from using chlorthalidone even after it was selected at lower doses to be the diuretic of choice in three major National Institutes of Health-funded hypertension trials – the SHEP, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), and Systolic Blood Pressure Intervention Trial (SPRINT) studies.

The pharmacokinetic profile of chlorthalidone clearly differs from that of hydrochlorothiazide. Importantly, chlorthalidone has a much longer duration of antihypertensive effect than that of hydrochlorothiazide and is more potent at comparable dosages. When used in small doses (e.g., 12.5 mg per day), hydrochlorothiazide may not provide a full 24-hour effect on blood pressure in some patients in contrast to the long action of chlorthalidone, although these differences may be overcome if larger doses of hydrochlorothiazide are employed. Whether other clinically important differences exist between the two drugs is uncertain despite various speculations to that effect.

The review provided by Pareek et al shows that the antihypertensive effect of chlorthalidone at 6.25 mg per day is not significantly different from that of selected representatives of other antihypertensive drug classes when used in various combinations. In addition, the metabolic side effects of chlorthalidone at this dose are minimal. Other published data have indicated that chlorthalidone is useful in most hypertensive individuals, including diabetics. Based on the available evidence, I would conclude that chlorthalidone should be preferred over hydrochlorothiazide in the treatment of hypertension.

Combination therapy is particularly important in hypertension since in more than one-half of individuals, two or more antihypertensive drugs are required to control the blood pressure to less than 140/90 mm Hg. Combination preparations that involve two or three

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antihypertensive drugs are of practical value in reducing cost and improving adherence to therapy. Despite the demonstrated efficacy of blood pressure lowering in reducing mortality and morbidity from cardiovascular and renal diseases irrespective of age, gender, race, ethnicity, socioeconomic status, or the presence or

absence of cardiovascular disease, less than one-third of hypertensive persons worldwide have their blood pressure controlled to less than 140/90 mm Hg. With a prevalence of more than 1.2 billion persons worldwide, hypertension remains a serious public health problem that demands intensive efforts in every country for its control.