CHAPTER I

I. Introduction

I.1. General introduction

I.1.1. Commencement

Hypertension is the most common cardiovascular disease. As many as 43 million adults in the United States have systolic and/or diastolic blood pressure above 140/90.

Elevated arterial pressure causes pathological changes in the vasculature and hypertrophy of the left ventricle. As a consequence, hypertension is the principal cause of stroke, leads to diseases of the coronary arteries with myocardial infraction, sudden cardiac death, major contributor to cardiac failure, renal insufficiency, and dissecting aneurysm of the aorta [1].

Hypertension is defined conventionally as blood pressure ≥ 140/90; this serves to characterize a group of patients who carry a risk of hypertension-related cardiovascular diseases that is high enough to merit medical attention. However, from the standpoint of health promotion, it should be noted that the risk of both fatal and nonfatal cardiovascular diseases in adults is lowest with systolic blood pressures of less than 120 mm Hg and diastolic of less than 80 mm Hg; these risks increase progressively with higher levels of both systolic and diastolic blood pressure.

Blood pressure is expressed in terms of the arterial systolic and diastolic pressures. Since many factors influence blood pressure, it is not possible to define normality or abnormality precisely using only the figures

for systolic and diastolic pressures. An arbitrary definition of normal adult blood pressure provided by the World Health Organization (WHO) is a systolic pressure equal to or below 140 mm Hg (18.7 kPa) (Kilopascal-Cal, SI unit of blood pressure); together with a diastolic pressure equal to or below 90 mm Hg (12 kPa). Hypertension in adults is also arbitrarily defined by WHO as a systolic pressure equal to or greater than 160 mm Hg (21.3 kPa) and a diastolic pressure (fifth phase) equal to or greater than 95 mm Hg (12.7 kPa). Blood pressure is still expressed in mm Hg and this is the unit used throughout the world [2].

Life expectancy is reduced in patients with elevated blood pressure. Evidence has accumulated that reduction of elevated blood pressure reduces the risks of morbidity and mortality.

The drugs used in the treatment of hypertension belong to groups with distinct pharmacological actions, though the precise mode of action of some of them is not as yet fully understood.

The aim of an antihypertensive treatment is to attain a blood pressure level within the normal limits. To achieve this, an uninterrupted life-long treatment with antihypertensive drug is necessary. This universally accepted treatment, designed by the Joint National Committee on Detection Evaluation and Treatment of High Blood Pressure [3] is based on the fact that, in most cases it is not urgent to decrease the blood pressure. Therefore, this treatment should be initiated by the supply of small doses of a drug of moderate effectiveness. These doses should be increased until adverse reactions appear. If this is the case, other drugs must be added in a successive way, according to necessity. Therefore, it may be necessary to give two, three or even four different drugs.

In this way a common so-called staggered treatment in triple therapeutic form can be initiated with a diuretic or a drug of similar effect

such as prazosin (α-blocker), followed by an antihypertensive drug (direct vasodilator) and an angiotensin system inhibitor. In view of the toxicity of certain antihypertensive drugs, the doses must be carefully tailored to each individual and it is recommended that a temporary follow-up of the serum concentration is carried out.

I.1.2. Investigation of the studied drugs

I.I. Captopril

The captopril (CAP) story began in 1971 with a report [4]. Captopril is an active inhibitor of the angiotensin-converting enzyme (ACE) has been widely used for the treatment of hypertensive diseases [5] as such or in combination with other drugs; this thiol drug can also be used to moderate heart failure [6]. The pK_a of the carboxylate of captopril is 3.7 [7]. Captopril in an aqueous solution undergoes an oxygen facilitated, first order, free radical; oxidation at its thiol to yield captopril disulphide [8]. It is absorbed rapidly as indicated by measurable blood levels of the drug 15 min after ingestion [9]. These findings are compatible with reports of the onset of antihypertensive activity as soon as 15 min after a single oral dose [10] in hypertensive patients and with the rapid onset of blockade of angiotensin induced increases in blood pressure in healthy subjects [11]. Other studies revealed that the captopril metabolites included its dimmer disulphide and the mixed disulphide with glutathione, cystene, and serum albumin [12]. The compound is given orally as a tablet.