CHAPTER-III

INTRODUCTION

Despite advances in the understanding of central and peripheral mechanisms involved in the control of arterial blood pressure, drugs for the treatment of hypertension have largely evolved empirically (Relman, 1980). In consequence, an agent acting preferentially on vascular sensitivity should be of therapeutic interest (Grimm et al., 1981).

The diuretics have been used successfully for many years as a first line of treatment for the hypertension but they can produce several unwanted side effects. Indapamide, an hemihydrate and a non-thiazide indoline derivative of chlorosulphonamide, was synthesized in an attempt to produce a molecule which would have a maximum antihypertensive effect, but minimum diuretic activity and side effects (Campbell and Moore, 1981).

Chemically it is analogous with chlorthalidone. The nature of the antihypertensive effect of indapamide is still debatable, its efficacy has been described as largely dependent on its diuretic action (Onesti et al., 1977b; Bing et al., 1981; Chalmers et al., 1982). Several studies of hypertensive patients have shown indapamide to be unique among diuretics with regard to its ability to

induce a significant reduction in arterial pressure at doses which produce little or no diuresis (Fernandes et al.,1977; Kelly and Hamilton, 1977; Uhlich et al., 1977). Therefore, it has been hypothesized that the antihypertensive action of indapamide may also be due to some alternative mechanism(s).

Indapamide is particularly a promising compound for the treatment of hypertension since it can be given on a once a day basis and in the recommended doses, has minimal diuretic properties and causes no significant metabolic disturbances. Its mode of action remains controversial but current evidence suggests that vasodilatation may be the dominant mechanism since it has been shown to exert effective control of hypertension in animals (Kyncl et al.,1975) and in man (Royer, 1976).

Indapamide has been shown to be a potent long-lasting antihypertensive agent when used alone or in combination for all degrees of hypertension (Campbell and Moore, 1981). Its mechanism of action has not been fully elucidated although antihypertensive activity in man is associated with a reduced vascular resistance (Canicave and Lesbre, 1977). It decreases in vitro the contraction of vascular strips elicited by ANG and catecholamines (Gargouil and Mironneau, 1977).

It has been shown in the portal vein that indapamide may act on plasma membranes of smooth muscle cells by reducing the transmembrane calcium current and consequently the contraction (Mironneau and Gargouil, 1979; Mironneau et al., 1981). Further preliminary indications that indapamide acts on calcium fluxes have been reported by Schleiffer et al.(1980). They found that incubation of rat thoracic aorta with indapamide significantly reduced the ANG-stimulated increase in Ca^{++} influx. Therefore, a direct effect of indapamide upon blood vessels with an emphasis on calcium entry blocking properties has been claimed to distinguish indapamide from currently used diuretics.

Recent studies have suggested that essential hypertension is associated with exaggerated cardiovascular reactivity to NA in the presence of normal or sometimes even high sympathetic renin activity and normal body sodium volume state. This abnormally high NA reactivity is corrected by indapamide without accompanying increase in endogenous plasma NA level. This action of indapamide might be mediated by inhibition of inward calcium current in vascular smooth muscle cells which may be lowering the availability of intracellular calcium which is necessary for excitation-contraction coupling. Other possible though speculative

mechanisms would be reduction in sodium or water content of blood vessel wall or stimulation of vasodilator PG (Grimm et al., 1981).

Animal studies employing renal hypertensive cats and DOCA hypertensive rats have demonstrated the antihypertensive properties of indapamide (Finch et al.,1977a,b). The data indicate that this agent has diuretic properties with a possible extra-renal component (Beregi, 1977).

Indapamide is a potent new antihypertensive diuretic that has been evaluated in more than 2000 patients and normal volunteers in several countries. Chemically it has the sulfonamide moiety in common with some diuretics, but it also has an indoline moiety, which makes it unique in this respect. A nitrogen-to-nitrogen moiety suggest a possible similarity to hydrallazine, which has a direct vascular effect (Frank et al., 1983).

When used as the sole treatment, in mild to moderate hypertension, it is as effective as thiazide diuretics and beta-adrenergic blocking agents, methyldopa, and other antihypertensive agents. While such findings need confirmation, it appears that indapamide shares the potential with other diuretic agents to induce electrolyte and other metabolic abnormalities, although it may do so with less frequency or severity.

Although the ability of indapamide to relax vascular smooth muscle and decrease peripheral vascular resistance has been demonstrated in various in vitro and in vivo investigations, further study is required to clarify the extent to which the antihypertensive efficacy of indapamide can be attributed to actions other than its diuretic effect.

The effects of indapamide on in vivo vascular reactivity have been studied both in laboratory animals and in man. In rats, indapamide (usually 10 mg/kg daily) decreased pressor response to oxotremorine, NA and TYR, whereas pre-treatment with hydrochlorothiazide, 5 mg/kg intra-peritoneally did not decrease pressor response to the latter 2 agents. In patients with hypertension, vascular reactivity (i.e. pressor responsiveness) to PE, NA and ANG II were decreased after indapamide, 2.5 to 5 mg daily for 2 to 6 weeks. In small numbers of patients with hypertension, indapamide, 2.5 mg daily for 6 to 12 weeks was shown to increase muscle blood flow, and decrease limb vascular resistance, total peripheral resistance, and peripheral resistance 'index'. However, the non-invasive techniques and indirect methods of assessment used in the majority of these studies necessitate cautious interpretation of these findings (Chaffman et al., 1984).

Many studies have demonstrated the ability of renal tissues to generate PGs. Although the exact inter-relationships between PG metabolism (primarily that of PGs-E_2 and I_2) and blood pressure have not been elucidated, it is likely that some PGs play some part in the overall regulation of blood pressure (Lant, 1981; Campbell, 1983).

Thus, indapamide appears to offer a suitable alternative to more established drugs as a first line treatment in patients with mild to moderate hypertension. Whether it differs significantly from other diuretics when used as antihypertensive therapy, either in its mode of action or its side effect profile, needs further clarification.

Therefore, the present study was undertaken to study the mechanism of antihypertensive action of indapamide especially in relation to the production of PGs, calcium interfering property and vascular reactivity in vivo and in vitro.