CHAPTER-VII

S U M M A R Y

Indapamide, a new antihypertensive diuretic has been shown to be a potent long-lasting hypotensive agent when used alone or in combination for all degrees of hypertension. Its mechanism of action has not been fully elucidated. Further study is required to clarify the extent to which the antihypertensive efficacy to indapamide can be attributed to actions other than its diuretic effects. Therefore, the present investigation 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.

1. Indapamide (oral treatment) did not have any action on the blood pressure or heart rate in normotensive rats. The drug lowered the blood pressure ($P < 0.01$) and increased ($P < 0.05$) the heart rate in renal DOCA/salt hypertensive rats.

2. Indapamide did not seem to lower the blood pressure through PGs as indomethacin did not reverse the blood pressure lowering effect of indapamide.

3. Indapamide further lowered the blood pressure in the presence of verapamil suggesting that it has some other action in addition to verapamil-like.

4. In the presence of hydrallazine, there was no further lowering of blood pressure by indapamide suggesting that indapamide may also have direct vascular site of action.

5. In hypertensive but not normotensive rats, indapamide reduced pressor responses to NA and ANG following indomethacin treatment, to NA and PE following verapamil treatment and to NA following hydrallazine treatment suggesting that vascular reactivity to pressor stimuli is reduced by indapamide.

6. Indapamide induced increase in heart rate in hypertensive rats was blocked by indomethacin or verapamil treatment.

7. In hypertensive rats, reflex bradycardia to various pressor agents was greater following indapamide treatment suggesting that indapamide interferes with baro-receptor reflex activity. This action of indapamide was not observed in indomethacin or verapamil treated hypertensive rats.

<u>In vitro studies (rat tissues)</u>

8. Indapamide inhibited responses to NA, KCl, $CaCl_2$, TYR, ANG and 5-HT, in vascular (aorta, portal vein) and non-vascular smooth muscle (vas deferens). It is possible that indapamide inhibits the ionic

movement of calcium or might be depleting Ca^{2+} stores after prolonged treatment which results in decreased reactivity to various contractile agents. Higher dose was necessary to block responses in vas deferens suggesting greater selectivity of indapamide for vascular smooth muscle.

9. Indapamide further inhibited responses to K^+ in rat aorta and vas deferens in the presence of verapamil suggesting that both acted synergistically to one another. Indapamide might also partly be acting through inhibition of NA release by K^+. The same might be true for inhibition of TYR and ANG responses by indapamide in vas deferens. Blockade of neuronal uptake of tyramine by indapamide could be an additional mechanism for the inhibitory effect of indapamide on responses to TYR.

10. Indomethacin did not modify indapamide-induced inhibition of NA responses in aorta or vas deferens suggesting that PGs are not directly responsible for indapamide-induced inhibition of NA responses.

11. It is concluded that indapamide decreases blood pressure through relaxation of vascular smooth muscle. Direct effect on vascular smooth muscle may be through the ability of indapamide to decrease calcium inward flow, vascular reactivity and peripheral arterial resistance.