INTRODUCTION

CALCIUM ANTAGONISTS

Several drugs with similar pharmacological effects, although with various chemical formulae, were recently grouped together as calcium antagonists drugs (Fleckenstein, 1977).

Calcium antagonists represent a new class of drugs of considerable theoretical and practical importance. As implied by the name, they interfere with the normal function of Ca^{++} in the body including that in the excitation-contraction coupling in smooth muscle and in cardiac muscle (Zsoter, 1980).

Over twenty years ago two drugs prenylamine, an amphetamine-like drug, and verapamil, a papaverine derivative were introduced from Germany to treat angina. It was shown experimentaly that they acted in the same way as Ringer's calcium free infusion i.e. they mimicked the cardiac effects of calcium deficiency. Subsequently it was shown that the pharmacological basis of action of verapamil and nifedipine was to inhibit calcium entry into cardiac cells and smooth muscle. The term Ca^{++} antagonists was introduced in 1969 for agents that prevented the

entry of calcium from the extracellular fluid into the cell via postulated pores or channels. Hence these drugs have also been called calcium entry or calcium channel, blockers (Lewis, 1982).

Ca^{++} antagonists have been extensively studied with cardiac and vascular muscle and are used for treatment of hypertension and ischaemic heart disease, Recently, it has been shown that these antagonists are active in the prevention of exercise-induced asthma. These clinical data suggest that Ca^{++} antagonists may have a direct effect on both vascular and respiratory muscle (Cerrina et al., 1983). Furthermore, attension has been focused on their use as clinically efficacious agents for disorders of the respiratory system, such as bronchial asthma (Weichman et al., 1983).

These compounds interfere with the calcium influx needed to translate membrane depolarization into cellular contractile events. As a result of this action, calcium channel blockers inhibit the contractile mechanism in myocardial muscle and smooth muscle in the blood vessels, myometrium, urinary tract and oesophagus (Russi et al., 1983).

Within the last several years the list of agents

which have been classified as "Ca^{++} channel blockers" has grown from essentially three -nifedipine, verapamil, and diltiazem- to well over a hundred, including a number of nifedipine analogous, as well as caroverine, lidoflazine, FR 7534, and cinnarizine (Weishaar, 1984).

However, the drugs of this class available on the market still lack the pharmacodynamic and pharmacokinetic profile most appropriate for their current therapeutic applications. Improvements can be made in two directions. Firstly, the pharmacokinetic properties of future calcium antagonists should be tailored to better satisfaction of the requirements of patients and physicians. Secondly, special efforts should be directed towards the design of calcium antagonists with the most appropriate pharmacological and pharmacodynamic properties for the treatment of specific diseases (Spedding & Cavero, 1984). They believed that ideal drugs should normalize pathological processes without altering physiological functions. Calcium antagonists may become a therapeutic class which, if well exploited, can satisfy this essential requirement and achieve a desirable high degree of safety and effectiveness (Spedding & Cavero, 1984).

It is probably a historic accident that the calcium channel blockers were developed as cardiovascular drugs (Katz et al., 1984).