INTRODUCTION
Hypertension is a general public health problem. It is one of the major risk factors for cardiovascular morbidity and mortality, which accounts for 20-50% of all deaths (Carola Bardage and Isacson, 2000).

The second half of the twentieth century has seen a progressive decrease in cardiovascular mortality in North America, Western Europe, Japan and Australasia. Recent surveys in the USA have demonstrated that whereas 10% of the hypertensive subjects had their blood pressure lowered to below 140/90 mm Hg in 1976-80, by 1988-91 the proportion had risen to 27% (Burt et al., 1995). It is important to note that this leaves over 70% of hypertensive subjects with imperfect control (or no treatment at all) and that there are worrying signs that the rate of improvement has plateaued or even reversed in some cases. In USA there is recent evidence which indicates a rise in age-adjusted stroke mortality rate and decrease in the rate of decline of coronary heart disease (Vidal et al., 1997).

Joint National Committee (JNC VI 1997) guidelines recommend five classes of drugs as first line treatment choices: Diuretics, Beta blockers, calcium channel antagonists, alpha-1 adrenoceptor antagonists and ACE inhibitors/Angiotensin II receptor antagonists.

The WHO-ISH guidelines (1999) lay emphasis on individualization of drug treatment. The physician should determine the absolute level of cardiovascular risk i.e., risk based not only on blood pressure but also on gender, age, serum lipoprotein levels, smoking habits, diabetes and family history of cardiovascular disease before initiating treatment (Opie, 1993).

It has been observed that no single drug or drug class currently available will successfully and acceptably control blood pressure in more than 40-60% of
patients with hypertension (Neaton et al., 1993). So the search for new drugs or drug combinations is still going on.

Adherence with the prescribed treatment regimen is a key factor in achieving and maintaining satisfactory control of blood pressure and poor compliance with prescribed anti-hypertensive drug regimens is a prevalent cause of unsatisfactory control of blood pressure (Waeber et al., 1997). Newer strategies are being developed to increase compliance and one of them is once per day dose. The concept of trough-peak ratio is now universally accepted and is viewed as a guide to the appropriateness of the dose and dosing frequency.

Anti hypertensives with trough-peak ratios of > 50% are appropriate for once a day dosing and ensure good compliance. (Leszek et al., 1995; Elliot, 1996; McIntyre et al, 1997).

Another strategy to improve compliance is use of combination therapy (Menard 1993; Cappucio et al., 1995). JNC VI (1997) lists them as possible first line agent in the treatment of moderate to severe hypertension. Combination therapy with the available drug classes has been shown to produce blood pressure reductions that are greater than those produced by any group of individual agents used alone.

In the HOT study, combination therapy was necessary in 70% of participants to achieve and maintain tight target blood pressure levels (Hansson 1995; Hansson et al., 1998). Effective drug combinations utilise drugs from different classes in order to obtain the additive hypotensive effect that comes from combining drugs with different primary actions, while minimizing the compensation that limit the fall in blood pressure.
The combination of a CCB and an ACE inhibitor or Ang II receptor antagonist was considered the most promising offering additional benefit over the others (Amir et al., 1994; Roberto 1997; Messerli et al., 2000).

Calcium antagonists have vaso-dilating activity which is derived from the inhibition of calcium entry into myocytes and smooth muscle cells of arteries (Ambrosioni, 1996). Involvement of renin-angiotensin system in the aetiology of many cardiovascular and renal diseases provides a rationale for targeting this system in the treatment of hypertension (Ruiloze, 2000).

ACE inhibitors are therefore considered as very effective antihypertensive agents. But now angiotensin II (AT\textsubscript{1}) receptor blockers provide a novel alternate to ACE inhibitors. ACE inhibitors are competitive inhibitors of ACE so their effects can be overcome by high levels of angiotensin I, which occurs after ACE inhibition due to removal of the negative feedback effect of angiotensin II on renal renin release.

ACE inhibitors are also unable to block the production of angiotensin II by non-ACE mediated pathways. Furthermore ACE is not a specific enzyme, its inhibition therefore has effects on other substances such as bradykinin leading to class specific side effects like cough associated with ACE inhibitors (Israelii et al, 1992; Lacourciere et al., 1994).

AT\textsubscript{1} receptor blockers like losartan, candesartan bind to the AT\textsubscript{1} receptor, thereby providing more complete blockade of the negative cardiovascular effects of angiotensin II than is possible with ACE inhibitors without inducing the side effect of cough. Early clinical studies demonstrate that AT\textsubscript{1} receptor blockers produce at least the same degree of target organ protection as ACE inhibitors. Unlike ACE inhibitors, they do not prevent the activity of angiotensin II on AT\textsubscript{2} receptors in the
heart, which is thought to reduce cardiac remodelling (Timmermans et al., 1991; Smith et al., 1992; Lever 1993; Hollengberg, 2000; Johnston, 2000).

Therefore a fixed dose combination of a calcium antagonist and an Ang II AT$_1$ receptor antagonist holds great promise in the management of hypertension. A fixed dose combination of amlodipine (5 mg) and losartan (50 mg) is available in India under trade name of losar-A but the clinical data pertaining to the combination was not accessible.

Therefore the present study was planned to evaluate the combination of a calcium channel blocker (amlodipine) and Angiotensin II AT$_1$ antagonist (losartan) with regards to their hemodynamic effects and adverse events in normotensive males and if feasible in mild to moderate hypertensive patients upon administration for a total of 4 week duration.