# Effect of Ketanserin in Chinese Elderlies

**Dr. LEE Yun-Cheong,** MB,FRCP(GLASG)
**Dr. NG Ngai-Sing,** MB, FRCP(GLASG,EDIN)
**Dr. CHAN Ming-Houng,** MB,MRCP(UK)
**Dr. KONG Tak-Kwan,** MB,MRCP(UK)

Geriatric Unit, Princess Margaret Hospital, Hong Kong

***Summary***

*The efficacy of a new anti-hypertensive agent, ketanserin is tested in 40 elderly hypertensives. It is found to be effective but gradual in its maximum effect. Major side-effects such as arrythmia are not encountered with careful monitor of the serum electrolytes - especially potassium. Its use with other antithrombotic agents must be treated with caution.*

**Introduction**

Various studies have shown that treatment of hypertension is definitely beneficial to the elderly[1,2,3,4,5,6]. However, controversy has arisen regarding to the choice of antihypertensives. Claims for various agents' efficacy in the elderly hypertensives have been proved or disproved. For instance, the use of B-adrenergic blockers, previously thought to be less effective [7] - is found now to be at least as effective as other agents in the elderly hypertensive[8] Similarly, the claim that calcium antagonists might be more effective in the elderly[9] has not been proven by other studies [10]. A preferential age-dependent antihypertensive action has been reported for a newer agent, ketanserin which is a serotonin antagonist as well as an alpha-adrenergic receptor blocker[11]. The antihypertensive action of ketanserin appears to be of slow onset and would take a period of 3 months to reach its maximum effect [12]. This might also be an additional advantage in the treatment of hypertension in the elderlies as too rapid a drop in the blood pressure control sometimes contribute to undesirable consequences [13,14]. This study looks at the efficacy of ketanserine in a group of Chinese elderlies with hypertension, either given as monotherapy or used in a combination therapy.

**Method**

Male and female patients above the age of 65 with hypertension (systolic above 160 and/or diastolic above 90) are included. Monotherapy (n = 25) with ketanserine 20mg twice a day is started for patients who are either untreated for at least 6 weeks prior to the run-in period; or for those patients having unpleasant or intolerable side effects on existing therapy and hence such drugs are taken off at the beginning of the run-in period. Combination therapy (n = 17) is given to those patients who are either not sufficiently controlled by existing therapy; or those who suffer unpleasant/intolerable side effects on existing therapy but inappropriate to stop existing therapy totally. The types of other antihypertensive agents given to the patients are listed in table 1. Patients are assessed by the attending geriatrician in every four weeks and any side effects observed were noted.

**TABLE 1**

| Drug | Number of patients given |
|---|---|
| Metoprolol | 5 |
| Idapamide | 2 |
| Prazosin | 2 |
| Methyldopa | 2 |
| Labetolol | 1 |
| Captopril | 1 |
| Metoprolol + methyldopa | 1 |
| Metoprolol + Idapamide | 1 |
| Metoprolol + Prazosin | 1 |
| Prazosin + Methyldopa | 1 |

The study is divided into 3 phases in which the first phase comprise of a 4 weeks run-in period when patients are given the placebo. Phase 2 consists of a period during which patients are given the active drug for an average of 12 weeks. At the end of the phase 2, patients are randomized to receiving either the active drug or the placebo for a further 12 weeks. Normal serum potassium level is ensured during the whole period of study. ECGs are checked at the beginning of phase I, II, III and the end of the trial. Renal function test, urate, blood sugar, serum total cholesterol, are checked at the beginning and the end of phase 2.

Statistics were carried out with a SPSS-PC microcomputer package where the Student t test and the Paired Student t test were utilized. Informed consent was given by all the patients taking part. The study was approved by the Ethical Committee of the Medical and Health Department of Hong Kong according to guidelines set in the Helsinki Declaration.

**Results**

42 patients with an age range of 65 to 85 (mean =73.86) entered the trial. There are 21 males and females respectively. There are 2 dropouts - one (male 81) due to an unrelated carcinoma of pancreas discovered during the treatment phase; the other (Female 77) had a discontinuation due to an acute myocardial infarction at the 12th week of active treatment, without any severe blood pressure drop documented. There is a total of 38 patients who enter the placebo controlled (3rd) phase of treatment.

At the beginning of Phase II (After 4 weeks run-in period) the patients have a mean systolic blood pressure of 203.5 mm Hg (1 Standard Deviation = 20.1) and a mean diastolic of 101.9 mm Hg (1 Standard Deviation = 9.5). At the end of 4 weeks, the mean systolic blood pressure is reduced to 193.3 mm Hg (1 S.D. = 21.6) ($P < 0.0001$)). The diastolic blood pressure is reduced to 95.3 mm Hg (1 S.D. = 11.5) ($P < 0.0001$). The drop is observed both in the monotherapy group as well as the combination therapy group ($P < 0.001$). At the end of 12th weeks, the mean systolic blood pressure dropped to 187.1 mmHg (1 S.D. = 22.5) ($P < 0.0001$) and diastolic blood pressure decreased to 91.3 mm Hg (1 S.D. = 6.1) ($P < 0.05$) FIGURE 1.

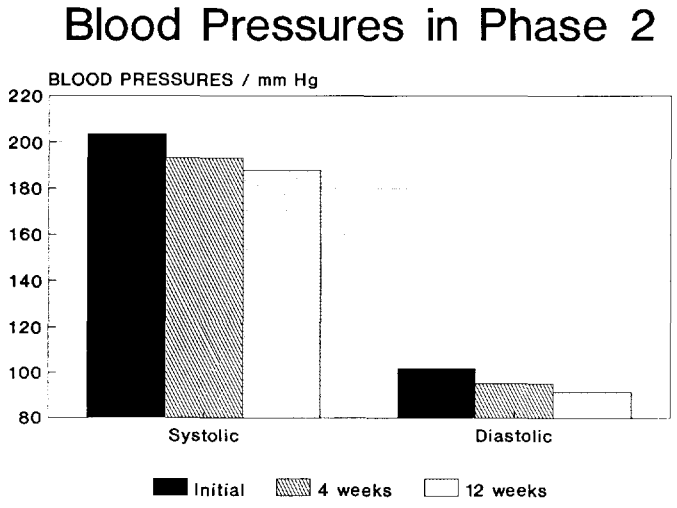


FIGURE 1

38 patients completed phase III of the trial. At the end of 12 weeks, the 19 patients who were given the active drug, have a further reduction of 5.6 mmHg (1 S.D. = 20.6) of the average systolic blood pressure while the group who was given placebo have an rise of 4.7 mmHg (1 S.D. = 16.9) in the systolic blood pressure ($P = 0.05$). At the same time, the active treatment group has a further reduction of 0.8 mmHg (1 S.D. = 7.4) in diastolic blood pressure; while the placebo group has an average increase of 2.1 mmHg (1 S.D. = 6.2). ($P = 0.78$). This is not statistically significant. FIGURE 2. Breaking down the group into monotherapy(n =24) showed that the systolic pressure was reduced by 3.8 mmHg (1 S.D. = 20) in the active treatment group (n = 12), compared to a rise of 0.75 mm Hg in the placebo group (1 S.D. = 16.6)($P = 0.28$); the diastolic pressure in the treatment group has a further fall of 0.79 mm Hg, while the placebo group had a rise of 1.6 mm Hg ($P = 0.17$). This again is not statistically significant.

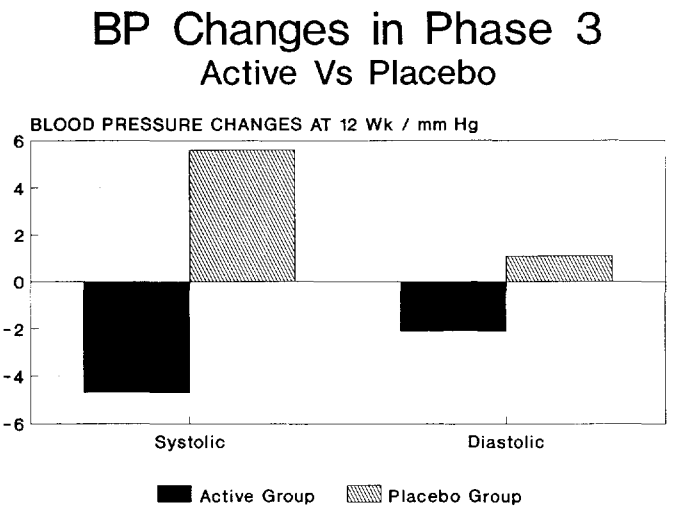


FIGURE 2

There were few side-effects encountered, mild malaise and dizziness being the commonest. (Table 2). However, one patient who was given concomitant low dose aspirin for transient ischaemic attack, has an attack of vitreous haemorrhage which led to the stopping of both aspirin and ketanserin - basing on the possible additive effects of the 2 drugs on the platelet function. No significant change in the renal function test, electrolytes, serum urate, blood sugar level, and total serum cholesterol was noted.

**TABLE 2**

| SIDE EFFECT | NO. OF PATIENT COMPLAINT |
|---|---|
| Malaise/tireness | 5 |
| Dizziness - non-postural | 3 |
| Dizziness - postural | 1 |
| Dry mouth | 1 |

**Discussions**

As an antihypertensive agent, ketanserin has unique properties for elderly patients where the response is more pronounce than the younger population [15]. Theoretically serotonin shows an increased vasoconstrictor properties in the presence of extensive atheroma. Antagonism of this effect may account for the greater antihypertensive effect of ketanserin in elderly subjects. The antiserotonin effect of the drug may also decrease serotonin-induced platelet aggregation[16] and hence be "protective" against thrombotic diseases so commonly found in the elderly. The rather gradual action which achieves the maximal blood pressure lowering at about 3 months [17] would have an additional advantage in the elderly where inappropriate treatment regimes with too rapid a blood pressure drop might result in additional side-effects [13, 14].

This study has shown that ketanserin is effective in the lowering the blood pressure of a group of Chinese elderly subjects and that a gradual blood pressure lowering occurs significantly after 4 weeks and even slightly extending beyond 12 weeks. No severe side-effects were found. One patient developed vitreous haemorrhage possibly as a result of additive side-effects of the use of aspirin and ketanserin - both known to have anti-platelet actions. Caution should hence be use when ketanserin is used simultaneously with other anti-thrombotic agents. Albeit coincidental, it is surprising that one patient actually developed an acute myocardial infarction during the treatment period of ketanserin. Nobel et al [17] has suggested that ketanserin might be protective against coronary arterial occlusion in patients having coronary artery stenoses. Larger studies must be conducted to prove or disprove this. No arrhythmia was encountered throughout the study, as potassium levels and ECGs are monitored carefully in the trial.

In conclusion, ketanserin offers an exciting new approach in the treatment of elderly hypertensives. Its effects are however not dramatic; and some of its theoretical benefits, like the prevention of coronary arterial thrombosis, is not substantiated. Its use in conjunction with other anti-thrombotic agents, should be treated with caution.

**References**


1. Veterans Administration Cooperative Study Group on antihypertensive agents. Circulation 1972; 45;991-1004.
2. Hypertension Detection and Follow-up program Cooperative Group. Five year findings: mortality by race, sex and age. J. Amer. Med. Ass. 1979; 242:2527-2529.
3. Australian National Blood Pressure Study. Treatment of mild hypertension in the elderly. Med. J. Aust. 1981; 2:398-402.
4. Kuramoto K., Matsushita S., Kuwajima I., Mutakami M. Prospective study on the treatment of mild hypertension in the aged. Jpn. Heart J. 1981; 22:75-85.
5. Amery A., Birkenhager W., Brixxol P. et al. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. Lancet 1985; i: 1349-1354.
6. Coope J., Warrender T.S. Randomized trial of treatment of hypertension in elderly patients in primary care. BMJ 1986; 293: 1145-1151.
7. Laragh VH. Vasoconstriction - volume analysis for understanding and treating hypertension, the use of renin and aldosterone profile. Amer. J. of Med. 55:261-274.1973.
8. Wilstrand J,Westergren G, Berglund G. Antihypertensive treatment with metoprolol or HCT in patients 60-75 years: a report from a double blind international multicentre study. J. of the Am M.Ass. 255: 1304-1310, 1986.
9. Muller RB, Bolli P, Erne P, Block LH, Kiowski W, et al. Antihypertensive therapy with the long-acting calcium antagonist nitrendipine. J. of Cardiovascular Pharmacology 6: S1073-1076 1984.
10. Hiramatsu K, Yamagishi F, Kubota T. Yamada T. Acute effects of the calcium antagonist, nifedipine on blood pressure, pulse rate, and the renin-angiotensin- aldosterone system in patients with essential hypertension. American Heart J 104: 1346-1350, 1982.
11. Vanhoutee P., Amery A, Birkenhager W., Breckenridge A., Buhler F, et al Serotonergic mechanisms in hypertension. Hypertension 11: 111-113, 1988.
12. Hedner T., Persson B, Berglund G. A comparative and long term evaluation of ketanserin in the treatment of hypertension. J. of Cardiovascular Pharmacology 7 (Suppl 7): S145-153, 1985.
13. Jackson G., Pierscianowski TA, Mahon W, Condon J. Inappropriate antihypertensive therapy in the elderly. Lancet, 1317-18 Dec 18 1990.
14. Jansen PAF, Gribnau FWJ, Schulte BPM, Poels EFJ. Contribution of inappropriate treatment for hypertension to pathogenesis of stroke in the elderly. BMJ Vol 293, 914-916 1986.
15. Breckenridge A. Ageing, Serotonin and Ketanserin. Drugs 36 (Suppl 1) 44-54 1988.
16. Amstein R., Fetkovska N., Ferracin F., Pletscher A., Buhler F. Serotonin Metabolism and Aged-related Effects of Antihypertensive Therapy with Ketanserin. Drugs 36 (Suppl. 1) 61-66 1988.
17. Noble M., Holland A.D., Letter. Prevention of atherosclerotic complications with ketanserin. Br Med J. Vol 298, 752 1989.