Cardiovascular Drugs and Therapy 4: 127–131 1990

SEROTONIN ANTAGONISM REDUCES THE ADVERSE SYMPTOMS OF BETA BLOCKADE

Krishnarao Korlipara,[1] Susan E. Gould,[2] Natalie A. Taylor,[2] Anthony Chandler[2]

[1]Pike View Medical Centre, Horwich, UK (representing the KTN 165 study group)
[2]Janssen Pharmaceutical Ltd, Grove, Wantage, Oxon, UK

SUMMARY. Beta-adrenoceptor antagonists (beta blockers) are a well-established first-line treatment for hypertension, but they have been associated with unwanted symptoms including cold extremities, lethargy, and nightmares. Ketanserin is a serotonin S_2-receptor antagonist that has previously been shown to reduce blood pressure in hypertensive patients by reducing systemic vascular resistance. Hypertensive patients whose sitting diastolic blood pressure was ≥ 95 mmHg, despite at least 4 weeks therapy with an optimal dose of beta blocker, were selected for the study. The beta-blocker dose remained constant throughout the study, but patients were randomly allocated to receive ketanserin 20 mg twice daily, ketanserin 40 mg twice daily, or bendrofluazide 5 mg each morning plus placebo at night in addition to the beta-blocker therapy. One hundred and forty two patients completed the symptom questionnaire at randomization and after 12 weeks treatment. The treatment groups were well matched for age, sex, weight, and blood pressure. Blood pressure was reduced significantly by all treatments, and there were no between-group differences. Bendrofluazide adversely affected alertness ($p < 0.05$) and concentration ($p < 0.01$) whereas ketanserin had no significant effect and the ketanserin 20 mg twice daily group had better concentration than the bendrofluazide group ($p < 0.05$). Ketanserin treatment reduced the incidence of nightmares ($p < 0.05$ for 20 mg twice daily and 40 mg twice daily) and was an improvement over bendrofluazide treatment in this respect ($p < 0.05$).

Leg pain on walking ($p < 0.01$) and at rest ($p < 0.05$) was worse on bendrofluazide, whereas ketanserin treatment 20 mg twice daily improved incidence of leg pain on walking ($p < 0.05$) and was an improvement over bendrofluazide treatment in this respect ($p < 0.05$). Incidence of flushing was reduced by ketanserin 40 mg twice daily ($p < 0.01$) more effectively than by bendrofluazide treatment ($p < 0.05$).

The present study indicated that serotonin antagonism by ketanserin can reduce the nightmares and sleep disturbance and reverse the deterioration in peripheral circulation that may accompany treatment with beta blockers.

KEY WORDS. beta blockers, ketanserin, bendrofluazide, elderly hypertensives

Beta-adrenoceptor antagonists (beta blockers) are well-established first-line treatment for hypertension, but they have been associated with unwanted symptoms including cold extremities, lethargy, and nightmares [1]. When a beta blocker alone fails to normalize blood pressure, a thiazide diuretic, such as bendrofluazide, is often added. Bendrofluazide has been reported to impair glucose tolerance, with increased reporting of impotence, lethargy, nausea, dizziness, and headache [2]. Use of a beta blocker plus a diuretic would be expected to produce the typical symptoms of both drug classes.

Ketanserin is a serotonin S_2-receptor antagonist that has previously been shown to reduce blood pressure in hypertensive patients [3] by reducing systemic vascular resistance.

In our previous study of hypertensive patients using the same symptom questionnaire [4], ketanserin increased the incidence of blurred vision, faintness, fatigue, and dry mouth, but reduced the incidence of sleeplessness, flushing, and cold hands and feet.

Methods

Hypertensive patients whose sitting diastolic blood pressure was ≥ 95 mmHg despite at least 4 weeks therapy with an optimal dose of beta blocker, were selected for the study. Antihypertensive medication other than a beta blocker was not permitted, and the beta-blocker dose remained constant throughout the study. Nine different beta blockers were used; the most frequently used was atenolol, received by 60% of patients. Patients received a single-blind placebo for 4 weeks, and those who still fulfilled the entry criteria were randomly allocated to receive ketanserin 20 mg twice daily, ketanserin 40 mg twice daily, or bendro-

Address for correspondence and reprint requests: Susan E. Gould, BSc, PhD, MRPharmS, Janssen Pharmaceutical Ltd, Grove, Wantage, Oxon, OX12 0DQ, UK

fluazide 5 mg each morning plus placebo at night, in addition to the beta-blocker therapy.

The following 32 symptoms were evaluated by a yes or no answer: faintness, dizziness, fatigue, lack of concentration, sleepiness, headaches, depression, sleeplessness, nightmares, dry mouth, blocked or runny nose, nausea/vomiting, stomach pain, sweating, flushes, blurred vision, tiredness after exercise, wheezing, chest pain, heart racing, nervousness, irritability, anxiety, alertness, pain in the legs on walking or at rest, night cramps, swollen ankles, cold hands and feet, and impotence. Bowel habit, urine output, activity, and appetite were quantified by a score.

For yes/no questions, shift tables were constructed and a McNamar test [5] was used to test significance within groups. It is usual to expect an increase in symptoms when giving a patient additional drug therapy, and in determining adverse effects any trends may be predictive of effects in larger populations. The probability values of a one-tailed test of significance are therefore quoted for symptoms reported. The relative odds of reporting a symptom on ketanserin versus bendrofluazide was calculated from a logistic regression analysis, adjusted for baseline using the GLIM package (the Generalized Linear Interaction Modelling statistics package designed by the working party of the Royal Statistical Society). For those questions containing more than two response categories, the percentage of patients in each category was calculated. The overall quality of life linear visual analogue score (VAS) was transformed by

$$X_i = \arcsin \sqrt{X}/100$$

(where X is the VAS score 0–100 scale)

to normalize the data prior to a one-way analysis of variance.

Results

One hundred and forty-two patients completed the symptom questionnaire at randomization and after 12 weeks treatment. The treatment groups were well matched for age, sex, weight, and blood pressure. The mean age was 58.5 (range 31–80) years and 57% of the patients were female. The mean body weight was 74.9 kg and sitting blood pressure was 175/106 mmHg.

Blood pressure was reduced significantly by all treatments, and there were no between-group differences. Heart rate was reduced by 3 beats/min on ketanserin. These data are reported in full elsewhere [6].

The most common symptoms after beta-blocker treatment were fatigue (63% of patients) and tiredness after exercise (63% of patients). Cold hands and feet were reported in 43% of patients. Thirty percent reported pains in the legs on waking and 16% reported nightmares. The overall quality of life scores and the scores for bowel habit, urine output, or activity were unaffected by any of the treatments.

Headache incidence decreased in all treatment groups, and this reached statistical significance for ketanserin 40 mg twice daily ($p < 0.01$ McNamar within group) and bendrofluazide ($p < 0.05$) (Figure 1). The incidence of fatigue was reduced slightly by ke-

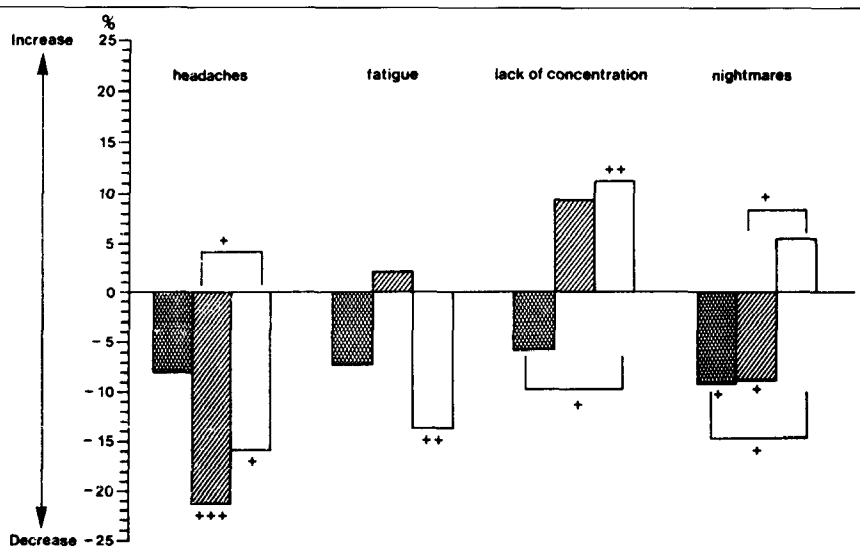

Fig. 1. Changes in percentages of patients reporting central nervous system symptoms after ketanserin 20 mg twice daily ▩, 40 mg twice daily ▨, or bendrofluazide 5 o.d. □ were added to beta-blocker treatment in hypertensive patients.
+ $p < 0.05$; ++ $p < 0.01$; +++ $p < 0.001$.

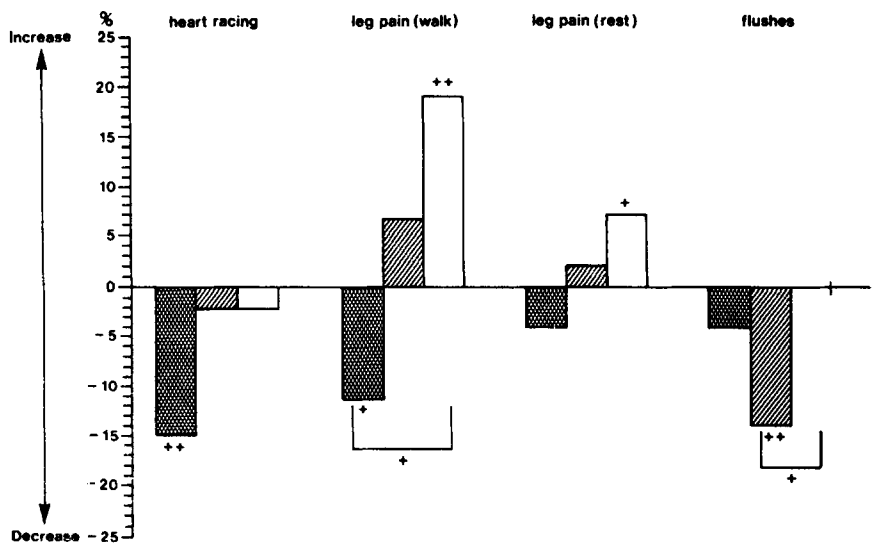

Fig. 2. Changes in percentages of patients reporting cardiovascular symptoms after ketanserin 20 mg twice daily ▒, 40 mg twice daily ▨, or bendrofluazide 5 mg o.d. □ were added to beta-blocker treatment in hypertensive patients.
+ $p < 0.05$; ++ $p < 0.01$.

tanserin 20 mg twice daily and by bendrofluazide ($p \leq 0.01$). Bendrofluazide adversely affected alertness ($p < 0.05$) and concentration ($p < 0.01$), whereas ketanserin had no significant effect and the ketanserin 20 mg twice daily group had better concentration than the bendrofluazide group ($p < 0.05$) (Figure 1). Ketanserin treatment reduced the incidence of nightmares ($p < 0.05$ for 20 mg twice daily and 40 mg twice daily) and was an improvement over bendrofluazide treatment in this respect ($p < 0.05$) (Figure 1).

Ketanserin 20 mg twice daily reduced the sensation of heart racing ($p < 0.01$) (Figure 2). Leg pain on walking ($p < 0.01$) and at rest ($p < 0.05$) were worse on bendrofluazide, whereas ketanserin treatment 20 mg twice daily improved the incidence of leg pain on walking ($p < 0.05$) and was an improvement over bendrofluazide treatment in this respect ($p < 0.05$). The incidence of flushing was reduced by ketanserin 40 mg twice daily ($p \leq 0.01$) more effectively than by bendrofluazide treatment ($p < 0.05$) (Figure 2).

The incidence of sweating was reduced by bendrofluazide ($p < 0.01$), while dry mouth was increased ($p < 0.05$) (Figure 3). The incidence of runny nose was decreased by ketanserin 20 mg twice daily ($p < 0.01$) and by bendrofluazide ($p < 0.01$), and that of swollen ankles was reduced by bendrofluazide compared with ketanserin 20 mg twice daily ($p < 0.05$) (Figure 3).

Discussion

Reporting of headaches was reduced over the 3-month study period on all treatments. Since this symptom also improved on placebo in our previous study [4], the improvement is unlikely to be treatment related. Reporting of fatigue is common during beta-blocker therapy [1]. It was not influenced by ketanserin, but bendrofluazide reduced the incidence of fatigue from 65% to 51% of patients, which is closer to that seen in untreated patients (48%) [4]. Tiredness after exercise was also more common in these patients (63%) than in our untreated patients (44%), but was not affected by any of the treatments. Bendrofluazide adversely affected alertness and concentration, and this may be analogous to the lethargy reported in the MRC trial [2]. Ketanserin is known to penetrate the central nervous system and reduced arousal acutely in psychomotor performance and electroencephalograph studies [3]. Ketanserin 40 mg twice daily only slightly reduced alertness in the present chronic study.

Nightmares were much more common after beta blockers (16% of patients) than in our untreated patients, (8%) as previously reported [1]. Beta blockers [7] and serotonin antagonists [8] reduce the duration of REM sleep. Beta blockers also disrupt sleep by increasing wakefulness and stage 1 [7,9], and

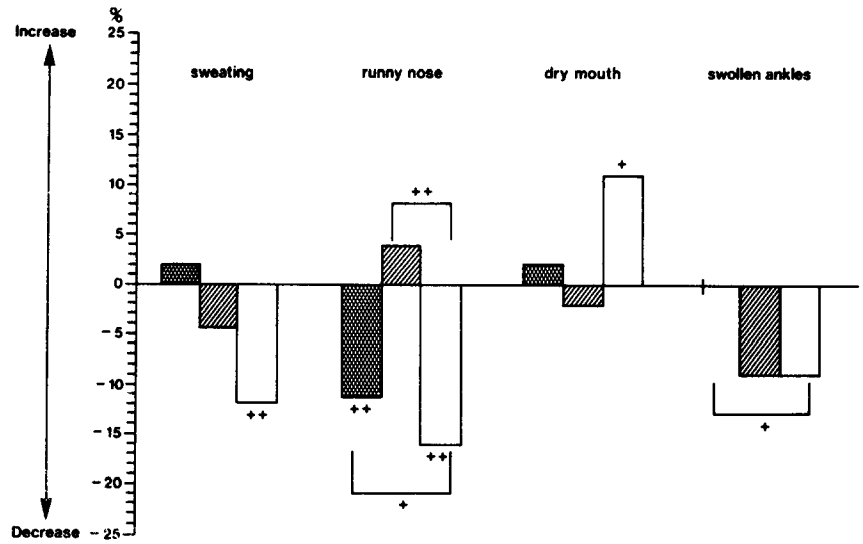

Fig. 3. Changes in percentages of patients reporting autonomic system symptoms after ketanserin 20 mg twice daily ▒, 40 mg twice daily ▨, or bendrofluazide 5 mg o.d. □ were added to beta-blocker treatment in hypertensive patients.
+ $p < 0.05$; ++ $p < 0.01$.

increase the likelihood of recalling dream episodes. Serotonin antagonists, in contrast, improve the continuity of sleep by decreasing stage 1 and prolonging deep (slow wave) sleep [8,10]. Thus the addition of ketanserin to a beta blocker reduces the awareness of vivid dreams and provides improved sleep quality, as previously reported [4,11].

Ketanserin 20 mg twice daily reduced the sensation of heart racing, and this may be related to the small reduction in heart rate seen in ketanserin-treated patients in this study. Pain in the legs on walking was slightly more common in beta-blocker-treated patients (30%) than in untreated patients (22%) [4] and may indicate an adverse effect of beta blockers on peripheral circulation, as previously reported [1]. Ketanserin improved pain in the legs on walking, in agreement with some previous studies [3]. Cold hands and feet were more common after beta blockers (43% of patients) than in untreated patients (32%) [4] in agreement with previous findings [1]. An improvement in symptoms of cold hands and feet after ketanserin treatment was seen in our previous study [4] but not in the present study of patients on beta blockers. There is evidence from other studies [3,12,13] of alleviation of symptoms of Raynaud's phenomenon and increased peripheral blood flow [12,14] after ketanserin. Flushing was reduced by ketanserin, in agreement with previous findings in hypertensive patients [4] and in patients with the carcinoid syndrome [15].

Bendrofluazide reduced sweating, dry mouth, and runny nose, probably reflecting a drying up of secretions resulting from its diuretic effect. Swollen ankles and feet were reduced by bendrofluazide, indicating its beneficial effects in edema. However, serious electrolyte imbalance may be caused, as was seen in this [6] and in other studies [2].

In conclusion, serotonin antagonism by ketanserin can reduce the nightmares and sleep disturbance and reverse the deterioration in peripheral circulation that may accompany treatment with beta blockers.

Acknowledgments

We are grateful to the following general practitioners who contributed patients to the study: Drs. Adams, Basu, Bochsler, Brown, Davies, Goodman, Harcup, Harrison, Hossain, Jones, Kane, Khan, Korlipara, Kukula, Kumar, Mainey, Pinheiro, Sagar, Saul, Saunders, Scott, and Shah. We appreciate the advice of Mrs. A. Whitehead (statistics), Mr. P. Welburn (quality of life questionnaires), and Dr. C. Idzikowski (assessment of sleep).

References

1. Cruickshank JM, Pritchard BN, eds. *Beta-Blockers in Clinical Practice.* London: Churchill Livingstone, 1988.
2. MRC Working Party on Mild to Moderate Hypertension. Adverse reactions to bendrofluazide and propranolol for the treatment of mild hypertension. *Lancet* 1981;2:539–543.

3. Vanhoutte P, Amery A, Birkenhager W, et al. Serotonergic mechanisms in hypertension—focus on the effects of ketanserin. *Hypertension* 1988;11:111–133.
4. Turner JF, Gould SE, Welburn PJ, et al. The effect of antihypertensive treatment on the assessment of well-being in a general practice population. *J Hypertens* 1987; 5(Suppl 5):S529–S531.
5. Seigel S. *Nonparametric Statistics for the Behavioral Sciences.* Tokyo: McGraw–Hill Publishers, 1956.
6. Korlipara K, Gould SE, Taylor NA, et al. Comparative trial of ketanserin or bendrofluazide as add-on therapy in hypertensive patients uncontrolled on a β-blocker alone. *Drugs*1988;36(Suppl 1):130–134.
7. Kostis JB, Rosen RC. Central nervous system effects of β-adrenergic blocking drugs: The role of ancillary properties. *Circulation* 1987;75(1):204–212.
8. Hammond G, Idzikowski C, Burton S, Jones R. The effects of chronic ritanserin treatment and withdrawal on sleep. *Psychopharmacology* 1988;96(Suppl):S295.
9. Dunleavy DLF, Maclean AW, Oswald I. Debrisoquine, guanethidine, propranolol and human sleep. *Psychopharmacology* 1971;21:101–110.
10. Idzikowski CI, Cowen PJ, Nutt D, et al. The effects of chronic ritanserin treatment on sleep and neuroendocrine response to L-tryptophan. *Psychopharmacology* 1987;93: 416–420.
11. The PACK Trial Group. Randomized trial of ketanserin for prevention of atherosclerotic complications. *Br Med J* 1989; 298:424–430.
12. Coffman JD, Dormandy JA, Murray GD, et al. International study of ketanserin in Raynaud's phenomenon. Data presented at International Symposium on Serotonin From Cell Biology to Pharmacology and Therapeutics. Florence, Italy, March 1989.
13. Tooke JE. Ketanserin and peripheral blood flow. In: *Serotonin Antagonists in Hypertension – Proceedings of an International Symposium.* Birmingham, 30th May, 1985. Update-Siebert, 1985.
14. Tomlinson IW. Monitoring cutaneous circulation in Raynaud's phenomenon with observations on ketanserin. *Adv Microcirculation* 1985;12:37–52.
15. Gustafsen J, Lendord A, Raskow H, Boesby S. Ketanserin versus placebo in carcinoid syndrome. *Scand J Gastroenterol* 1986;21:816–818.