Ketanserin in the treatment of traumatic vasospastic disease

VAGN HØJKJÆR LARSEN, JØRGEN FABRICIUS, GUNNER NIELSEN, KLAUS STAGIS HANSEN

Abstract

The specific serotonin receptor blocker ketanserin was given orally to 12 patients with traumatic vasospastic disease in a double blind crossover study. The effect of treatment was assessed by measuring finger systolic pressure and rewarming time after cold provocation and by medical interview and diaries. Median (range) percentage change in finger systolic pressure after cooling was 50 (0-100)% after treatment with ketanserin compared with 0 (0-90)% after placebo. Median (range) rewarming time after cooling decreased from 320 (236-972)s with placebo to 160 (88-404)s after treatment with ketanserin. These changes were not significant. Ninety five percent confidence intervals for difference between the treatments, however, showed that finger systolic pressure may be 80% better and rewarming time 256 seconds faster after treatment with ketanserin than after placebo. The number of attacks did not differ significantly between the two treatments. Two patients had a feeling of warmth in their hands during treatment with ketanserin.

The results suggest that orally administered ketanserin may improve digital circulation in patients with traumatic vasospastic disease, but larger numbers of patients are required to assess the true effect of treatment with ketanserin in this disease.

Introduction

Serotonin (5-hydroxytryptamine) is a vasoconstrictor synthesised in the enterochromaffin cells of the gastrointestinal tract and in tryptaminergic neurones. Results of in vitro studies have suggested two different receptor binding sites: the S_1 receptor and the S_2 receptor.[1] The S_2 receptor is selectively blocked by ketanserin. Through blocking the S_2 receptor ketanserin antagonises vasoconstriction, blood platelet aggregation, and bronchoconstriction.[1 2]

Many early reports of treatment with ketanserin in patients with Raynaud's syndrome produced promising results.[3-5] In most trials the study population consisted of patients with syndromes of mixed aetiologies. Raynaud's syndrome of occupational origin, or traumatic vasospastic disease, develops in many workers after using vibrating tools for several years. Frequent attacks of pallor and deadness in the fingers prevent the worker from doing his job, especially during the winter. Improvement in the circulation of the fingers by medical treatment would thus be of special importance during this season. During the winter of 1983-4 we studied the effect of ketanserin in patients with traumatic vasospastic disease.

Patients and methods

Twelve men with traumatic vasospastic disease were studied. Nine were employed as welders in the same ship building factory, using pneumatic drills, chisels, and grinding machines for preparing and attaching iron plates. Two men were employed removing automobile brake linings using pneumatic chisels. One cabinet maker, who had been exposed to vibrations from saws, planes, and milling machines during every working day for 24 years, had changed to another job just before he was tested. The median age was 43 years (range 29-62), height 180 cm (range 163-190), and weight 83 kg (56-93). The median time before the development of symptoms was 12 years (range 2-20), and the median total time exposed to vibrating tools was 17 years (range 5-27). Except for disorders of their fingers, all patients were healthy. According to their own reports they were normally temperate in their consumption of alcohol. Eight of the 12 patients were smokers.

The investigation was carried out in accordance with the Helsinki II declaration, and all patients gave informed consent to join the study, which was approved by the local ethical committee.

The study was conducted as a double blind, fixed sample size trial with cross over. After two weeks' treatment with placebo the 12 patients were allocated by random number to receive either placebo or ketanserin for five weeks. This was followed by a second five week period with the opposite treatment. The dosage of ketanserin was 20 mg three times daily for the first week followed by four weeks at 40 mg three times daily. Tablets were identical in appearance, and changes in dosage were unknown to patients. The trial was carried out from December 1983 to April 1984. During this period the outdoor temperature never varied far from freezing point, with extremes ranging from $-4°$ to $+8°C$. Entry was coordinated so that nearly all patients were in the same trial week during the same calendar week.

Small diaries were given to the patients to be filled in daily and posted weekly to an independent evaluator. The patients were asked to record how often or how long they went out, how many attacks they had outside and inside, whether there was pain, and how many fingers were affected. On the final day of the week they were asked to describe whether they felt better, worse, or no different and whether they had experienced any side effects. The patients were interviewed by the investigator just before the study and at the end of each of the three stages. The effect of treatment and any side effects were recorded.

At the end of each stage finger systolic pressure and rewarming time after cooling were measured in each patient. A Medimatics SP-2 Plethysmograph with digital cooling was used. Before the tests patients rested in the supine position with their hands on the upper abdomen under a blanket at room temperature (22-24°C) for at least 15 minutes.

Finger systolic pressure was measured with a finger pressure cuff over the mid-phalanx and a mercury in rubber strain gauge on the fingertip (fig 1). Simultaneous measurements were made on an affected finger cooled by water perfusion through the cuff (FSP_{th}) and on an unaffected reference finger at ambient temperature (FSP_{ref}). Blood perfusion of the fingers was abolished during cooling by maintaining an occluding pressure in the cuff. Finger systolic pressure was determined after cooling for five minutes at 30°C ($FSP_{th\ 30}$) and at 10°C ($FSP_{th\ 10}$). Reduction in systolic pressure in the cooled finger was expressed as a percentage of the pressure at 30°C ($FSP_{th\ 30}$) using the formula of Olsen and Nielsen[6]:

$$\text{Percentage change in finger systolic pressure after cooling to 10°C for 5 minutes} = \frac{100 \times FSP_{th\ 10}}{FSP_{th\ 30} - (FSP_{ref\ 30} - FSP_{ref\ 10})}$$

$FSP_{ref\ 30}$ and $FSP_{ref\ 10}$ were the values in the reference finger when the test finger was cooled to 30°C and 10°C respectively, and the bracketed term in the formula served as a correction for changes in systemic blood pressure.

The temperature of the finger was monitored by a skin sensor (Type A-H4, El-Lab) placed between the finger and the cuff and connected to a potentiometer (Type du 3s, El-Lab), from which a temperature curve was recorded on the recorder of the plethysmograph. Rewarming time was defined as the time from cessation of cooling for 5 minutes at 10°C until the finger temperature had risen to 20°C.

In addition to a history typical of traumatic vasospastic disease, a requirement for entry into the study was that arterial spasms could be demonstrated objectively—that is, finger systolic pressure after cooling was zero.

At the end of each stage of the study serum creatinine and urea concentrations were measured to monitor kidney function, and alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase

Departments of Clinical Physiology and Occupational Medicine, Odense University Hospital, 5000 Odense, Denmark
VAGN HØJKJÆR LARSEN, MD, registrar
JØRGEN FABRICIUS, MD, PHD, professor of clinical physiology
GUNNER NIELSEN, MD, senior registrar
KLAUS STAGIS HANSEN, MD, registrar

Correspondence to: Dr Højkjær Larsen.

activities and albumin, cholesterol, and bilirubin concentrations were measured to assess liver function. As a test of compliance plasma concentrations of ketanserin were determined by high pressure liquid chromatography after treatment with the drug.

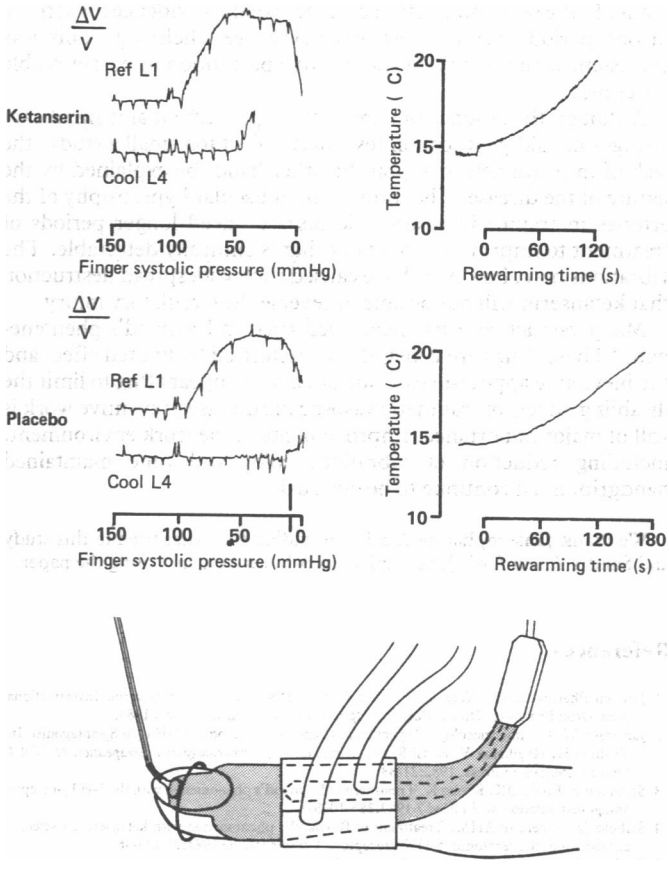

FIG 1—Plethysmographic and skin temperature recordings in one patient after cooling of the fourth left finger (L4) to 10°C. △ V/V=volume changes of the finger.

Statistical analysis followed the procedure described by Hills and Armitage.[7] Effect of treatment, period effect, and interaction between the treatments were tested by non-parametric statistics using Wilcoxon's test for paired data and the Mann-Whitney test for unpaired data. Power of the tests and sample size for detecting significant differences were calculated using parametric statistics. The 95% confidence intervals for differences between the medians were assessed according to the of *Documenta Geigy*.[8]

Results

Table I summarises the subjective data collected from the patients. One patient (case 8) did not wish to continue with the second treatment because of side effects experienced with the first which was ketanserin. Although he underwent cold provocation testing after five weeks without treatment, he has been left out of the statistical analysis. Two of the 11 remaining patients reported a feeling of warmth in their hands while they received ketanserin, but this was not accompanied by a reduction in pain. Adverse reactions were noted in six patients during treatment with ketanserin and in six during the placebo period. There was no significant difference between the two treatment periods in the number of attacks with deadness and pallor in the fingers.

After treatment with ketanserin the median percentage fall in finger systolic pressure after 5 minutes at 10°C was 50% (range 0-100%) compared with 0% (range 0-90%) after placebo (fig 2 and table II); the difference was not significant ($0{\cdot}05<p<0{\cdot}01$). The median time taken for the temperature of the finger to rise to 20°C after 5 minutes' cooling at 10°C was 160 s (range 88-404) after treatment with ketanserin (fig 2 and table II) and 320 s (range 236-972) after placebo; again, the difference was not significant ($0{\cdot}1<p<0{\cdot}2$). Period effect and interaction between the treatments were not significant in either test ($p>0{\cdot}1$).

Table III shows the 95% confidence intervals for difference of the medians, mean difference, power of the test, and required sample size. The true effect of treatment with ketanserin ranged with 95% confidence from −3 to 80% improvement in finger systolic pressure and from −32 to 256 s faster rewarming time.

TABLE I—*Effects of ketanserin and placebo reported by patients*

Patient No	Attacks per week		Side effects	
	Placebo	Ketanserin	Placebo	Ketanserin
1	36	32†		
2	4	4	Burning stomach	
3	0	0		Headache, sweating
4	10	7		Itching
5	2	13	Headache, constipation	Constipation, itching
6	9	4	Impotence	Impotence
7	12	9		
8	*	0†	*	Sedation, headache, constipation
9	0	0†		Itching
10	12	11		
11	6	3	Constipation	Constipation
12	11	3		

Attacks per week were compiled from diaries for the last two weeks of each treatment period. Order of treatment was random.
*Dropped out after final testing during treatment with ketanserin.
†Patients reported a subjective feeling of warm hands at interview at the end of the treatment period.

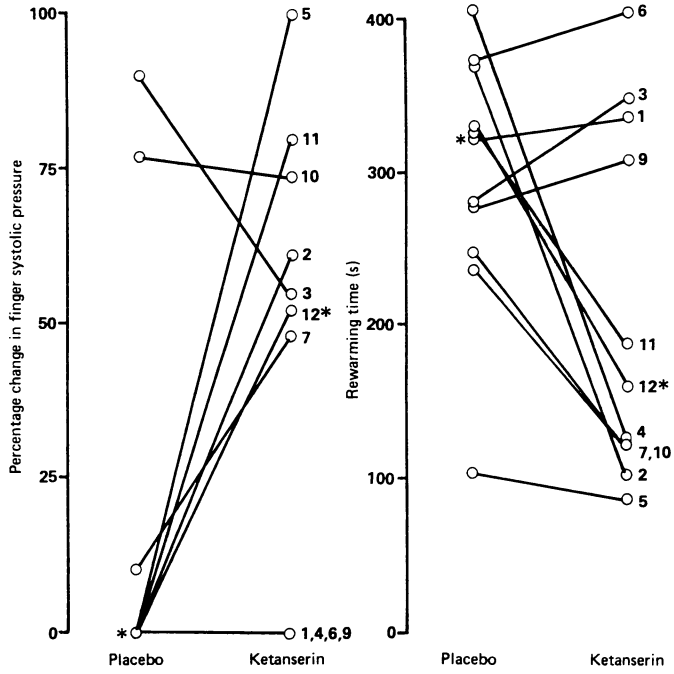

FIG 2—Individual values for finger systolic pressure after cooling to 10°C for 5 minutes and rewarming time from the same temperature after treatment with ketanserin and placebo. *Median values.

TABLE II—*Results of measurements of finger systolic pressure and rewarming time*

First Drug	Case No	Percentage change in finger systolic pressure after cooling to 10°C for 5 minutes		Time for finger temperature to rise to 20°C after 5 minutes cooling at 10°C (s)	
		Period 1	Period 2	Period 1	Period 2
Ketanserin	3	55	90	348	280
Ketanserin	4	0	0	128	972
Ketanserin	5	100	0	88	104
Ketanserin	6	0	0	440	372
Ketanserin	11	80	0	188	324
Placebo	1	0	0	320	336
Placebo	2	0	61	368	112
Placebo	7	10	48	236	124
Placebo	9	0	0	276	308
Placebo	10	77	74	248	124
Placebo	12	0	52	328	160

TABLE III—*Difference between ketanserin and placebo in results of finger systolic pressure and rewarming tests*

	Percentage in finger systolic pressure after cooling to 10°C for 5 minutes	Time for finger temperature to rise to 20°C after 5 minutes cooling at 10°C (s)
Difference between the median values	50	160
95% confidence intervals for difference between median values	−3 to +80	−32 to +256
Mean difference	26·6	133·8
Standard error of difference	12·7	78
Power of the test (1-β)	54%	34%
Required trial number (β=0·1, 2α=0·05)	28	40

Power of the tests and trial numbers have been calculated using the mean difference and standard error of difference.[7]

None of the patients found the benefit of the treatment so convincing that they wanted to continue after the end of the trial.

No changes in liver or kidney function were found after treatment with ketanserin.

Discussion

Traumatic vasospastic disease is difficult to diagnose between attacks. Because a typical history of disease was required for entry into this study, as well as occlusion at cold provocation, we believe that the risk of including subjects without the disease was small. Before the placebo run in period 11 of the 12 patients showed arterial spasms in response to different degrees of local cooling alone, whereas in one patient (case 3) spasms could be produced only after additional cooling of the arm in ice water for five minutes.

The lack of a significant difference between the treatments does not mean that a true difference did not exist (type II error). Especially when the sample size is small, the risk of not observing a true difference is considerable.[9,10] The 95% confidence intervals assessed the uncertainty of the difference in the medians as the true effect of treatment. To calculate the power of the test the mean difference and standard error of difference were calculated[7] (table III). The probability of observing the present mean difference as significant (power of the test) with 11 patients in the study was 54% in the finger systolic pressure test and 34% in the rewarming time test. Conventionally, 90% power of the test is required, and to reach this probability future studies will have to include 28 and 40 patients respectively.

Rewarming time was shown to be an appropriate test in traumatic vasospastic disease in a study in which the whole hand was cooled.[11] We used local digital cooling because we considered it important not to provoke severe arterial spasms if a difference between ketanserin and placebo were to be detectable. In this study seven of 11 patients had decreased rewarming times after treatment with ketanserin, which is consistent with improved skin perfusion found in other studies[2] and with the feeling of warmth in the hands reported by two patients.

Plasma concentrations of ketanserin were compared with known pharmacokinetic plasma decay curves, and in 11 and 12 cases values were in a range consistent with reasonable compliance. The plasma sample from one patient (case 4) taken three hours after the last stated consumption of medicine had no detectable ketanserin. During the treatment period, however, he had suffered from adverse reactions consistent with ketanserin, which suggests that he had previously taken his drugs. The patient (case 8) with the highest plasma concentration of ketanserin, at least twice the expected value, refused to continue into the second treatment period, having experienced intolerable restlessness, headache, and sluggishness during the first five week period. As with two other patients, he had a feeling of warmth in his hands after treatment.

The main side effects were itching and headache, and, except in case 8, the complaints were of only mild inconvenience. The overall incidence of side effects was 36% in patients taking placebo and 54% in those taking ketanserin; this compares with 17% and 24% respectively among 206 patients collected from previous double blind studies.[1] As itching was not mentioned in these earlier studies, this probably accounts for the higher overall incidence in our study.

Diaries and interviews provided little evidence for any difference between the two treatments. In three cases the diaries could not be assessed because record keeping was incomplete, erratic, or idiosyncratic. In the remaining sets of evaluable diaries evidence for activity in one period over another was never overwhelming. This was consistent with the patients' subjective perception of no noticeable difference.

Although the absence of subjective improvement and significant changes in cold provocation tests may reflect too small a study, the lack of improvement may, on the other hand, be explained by the nature of the disease. The intimal and muscular hypertrophy of the arteries in traumatic vasospastic disease[12] need longer periods of treatment to improve to an extent that is clinically detectable. The vibrations may, however, have caused such widespread destruction that ketanserin will not be able to reverse the circulatory injury.

Many vasoactive drugs have been tried in Raynaud's phenomenon.[13] These drugs are generally characterised by limited effect and the inevitable appearance of side effects. It appears that to limit the disabling effects of traumatic vasospastic disease preventive work is still of major importance. Improvements in the work environment, including reduction of vibration, cold, and time maintained handgrip, must continue to be our goal.

We thank Janssenpharma A/S for providing the drugs used in this study and Sandra A Guilford, Janssenpharma A/S, for help in writing the paper.

References

1 Janssen Pharmaceutica. *Ketanserin: A novel serotonin S_2-receptor blocking agent.* Investigational New Drug Brochure. 7th ed. Beerse, Belgium: Janssen Pharmaceutica, 1983.
2 Janssen PAJ. The pharmacology of specific, pure and potent serotonin 5-HT_2 or S_2-antagonist. In: Yoshida H, Hagiharaa Y, Ebasi S, eds. *Advances of pharmacology and therapeutics, II*, Vol 4. Oxford: Pergamon Press, 1982:21-33.
3 Stranden E, Roald OK, Krohg K. Treatment of Raynaud's phenomenon with the 5-HT_2-receptor antagonist ketanserin. *Br Med J* 1982;**285**:1069-71.
4 Seibold JR, Jageneau AHM. Treatment of Raynaud's phenomenon with ketanserin, a selective antagonist of the serotonin (5-HT_2) receptor. *Arthritis Rheum* 1984;**27**:139-46.
5 Roald OK, Seem E. Treatment of Raynaud's phenomenon with ketanserin in patients with connective tissue disorders. *Br Med J* 1984;**289**:577-9.
6 Olsen N, Nielsen SL. Diagnosis of Raynaud's phenomenon in quarrymen's traumatic vasospastic disease. *Scand J Work Environ Health* 1979;**5**:249-56.
7 Hills M, Armitage P. The two-period cross-over clinical trial. *Br J Clin Pharmacol* 1979;**8**:7-20.
8 Lensmer C, ed. *Documenta Geigy scientific tables.* 8th ed. Basel: Geigy, 1982:197.
9 Freiman JA, Chalmers TC, Smith H, Kuebler RR. The importance of beta, the type II error and sample size in the design and interpretation of the randomized control trial. *N Engl J Med* 1978;**229**:690-4.
10 Feinstein AR. Clinical biostatistics. XXXIV. The other side of "statistical significance": alpha, beta, delta and the calculation of sample size. *Clin Pharmacol Ther* 1975;**18**:491-505.
11 Juul C, Nielsen SL. Locally induced digital vasospasm detected by delayed rewarming in Raynaud's phenomenon of occupational origin. *Br J Ind Med* 1981;**38**:87-90.
12 Ashe WF, Cook WT, Old JW. Raynaud's phenomenon of occupational origin. *Arch Environ Health* 1962;**5**:333-42.
13 Bluntt RJ, Porter JM. Raynaud's Syndrome. *Semin Arthritis Rheum* 1981;**10**:282-308.

(Accepted 21 May 1986)

100 YEARS AGO

Professor Filatow recommends a very convenient method of taking temperature observations, which consists in first warming the thermometer (for example, by rubbing it with a pocket-handkerchief or a corner of the bed-clothes) to about 110° Fahr., and then quickly inserting it under the patient's axilla. The mercury falls rapidly to the body-temperature of the patient, and after one minute, or a little more, remains stationary, at a point only a little below the real temperature of the body. Between 100° and 104° Fahr., the difference, according to Filatow, is only 0·18° Fahr.; for temperatures nearer normal, a little more, 0·36° to 0·54° Fahr. Much time is saved by this method. Dr. Biedert, of Hagenau, has carefully examined this procedure, and finds that six minutes' time should be given, as otherwise quite misleading results may be obtained (*Berliner Klin. Wochenschr.*, No. 43). With this proviso, which goes far to neutralise the chief advantage alleged in its favour, the method is stated to be reliable. (*British Medical Journal* 1886;ii:1049.)