CLINICAL RESEARCH

# Treatment of Raynaud's phenomenon with the 5-$HT_2$-receptor antagonist ketanserin

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## Abstract

**The selective 5-hydroxytryptamine$_2$-(5-$HT_2$)-receptor-blocking agent ketanserin was given in a dose of 10 mg intravenously to nine patients with Raynaud's phenomenon. The effect on blood flow was assessed by photoplethysmography and measurements of skin temperature. Digital blood flow and skin temperature increased significantly after ketanserin injection, whereas the placebo (saline 9 g/l) had no such effect.**

**This study suggests that ketanserin may be useful in the treatment of Raynaud's phenomenon.**

## Introduction

Raynaud's phenomenon is characterised by episodic attacks of digital ischaemia precipitated by cold or stress. These vasospastic phenomena may be associated with other disorders such as connective-tissue disease, arteriosclerosis, thoracic outlet syndrome, drug-induced vasospasm, and traumatic vasospastic disease. Over 90% of patients, however, have no underlying abnormality, and their primary disorder is termed Raynaud's disease.[1]

The relative roles of autonomic, humoral, and local mechanisms in the pathophysiology of Raynaud's phenomenon remain unknown.[2] Halpern *et al*, however, suggested that the vasoactive substance serotonin might play some part in the aetiology.[3] We have therefore evaluated the effect on blood flow of the specific serotonin antagonist ketanserin in patients with severe vasospastic symptoms.

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## Patients and methods

We investigated seven women and two men with a mean age of 40·1 years (range 21-67 years). All gave informed consent. According to the criteria of Allan and Brown,[4] three were diagnosed as having Raynaud's phenomenon and six as having primary Raynaud's disease. The duration of symptoms varied from three to 30 years (table).

Measurements were carried out with the patients supine after resting for at least 30 minutes at a room temperature of 23-25°C and in an approximate air humidity of 50%. Photoplethysmography and changes in digital skin temperature were used to detect variations in finger blood flow. For these measurements a multichannel photoplethysmograph[5] including a sensitive temperature amplifier was used. The photoplethysmograph transducer ($12 \times 20 \times 8$ mm) contained a diode that emitted infrared light and an adjacent phototransistor that detected backscattered light (Optron, Inc, OPB 710). The transducer functioned on the reflectance principle of photoplethysmography,[6] the

*Details of patients studied*

| Case No | Sex and age (years) | Duration of symptoms (years) | Digital skin atrophy | Previous treatment | Associated disease |
|---|---|---|---|---|---|
| 1 | F 42 | 20 | + | Cervicodorsal and lumbar sympathectomy, methyldopa, guanethidine as regular intravenous blockade | Allergic rhinitis |
| 2 | F 27 | 15 | + | None | None |
| 3 | F 37 | 3 | Ulcer of tip of right index finger | None | None |
| 4 | M 46 | 4 | + | Lumbar sympathectomy | None |
| 5 | F 51 | 20 | + | Prednisone | Osteoarthritis |
| 6 | F 25 | 25 | – | Guanethidine as regular intravenous blockade | Urticaria |
| 7 | F 45 | 30 | Sclerodactyly, amputation of three distal phalanges of right hand | Cervicodorsal sympathectomy, terbutaline, prednisone | Scleroderma |
| 8 | F 21 | 10 | – | None | Bronchial asthma |
| 9 | M 67 | 25 | + | None | Arteriosclerosis obliterans |

phototransistor being sensitive to variations in infrared light passing through the tissue microcirculation. Infrared light has the advantage of being not greatly influenced by the degree of haemoglobin saturation of the blood. Furthermore, because of the low-power dissipation of the light-emitting diode there was only a negligible heating effect of the transducer. This contrasts with incandescent light sources, where the heating effect may present a problem.

Pulse volume and skin temperature were measured in the left index finger. A vein in the dorsum of the right hand was cannulated and 5 ml saline solution (9 g/l) injected as placebo followed about five minutes later by 10 mg ketanserin (R41468, Janssen Pharmaceutical, Beerse, Belgium) dissolved in a volume of 5 ml. Brachial blood pressure was measured before and at five-minute intervals for half an hour after the injections.

Statistical analysis was by Student's $t$ test for paired data, 5% being taken as the level of significance.

## Results

The effect of ketanserin on the circulation as judged by recordings of pulse volume appeared immediately or within three minutes after injection (fig 1). The increase in amplitude of the pulse volume varied from five to 20 times the basal value (fig 2). In most cases the peak value was recorded about three minutes after ketanserin injection, the mean increase at three minutes being 10·6±SEM 2·4 times the original resting pulse volume ($p<0·001$). The mean value decreased to 9·0±1·7 times the original volume at 10 minutes and to 7·7±1·3 times the original amplitude 20 minutes after the injection of ketanserin. One patient (case 6) did not respond to 10 mg ketanserin.

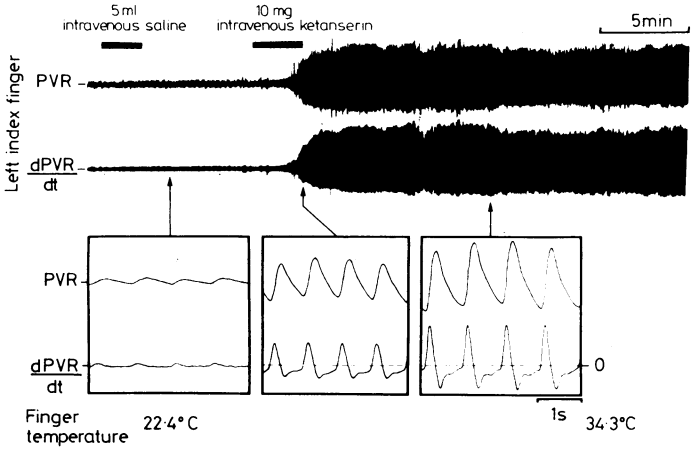


FIG 1—Effect on digital blood flow of intravenous injection of 5 ml saline and 10 mg ketanserin in case 1. Blood flow evaluated by recording digital pulse volume (PVR), its first-order derivative (dPVR/dt), and skin temperature. Recorded values close to average for whole group of patients.

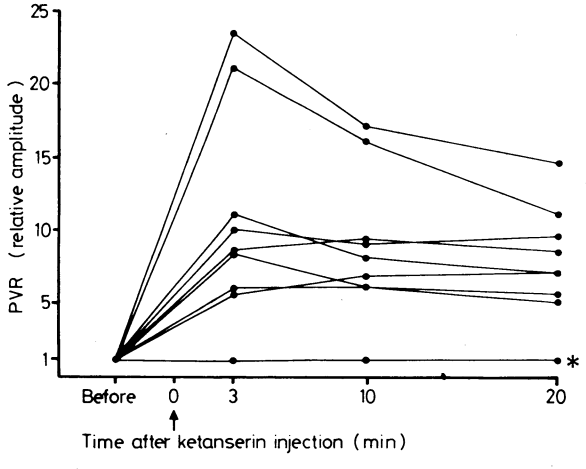


FIG 2—Summary of pulse volume recordings (PVR) in left index finger and after intravenous injection of 10 mg ketanserin (arrow) in patients with vasospastic disorders. Values on ordinate are relative to PVR before injection.
*Patient (case 6) with no measurable effect from dosage used in investigation.

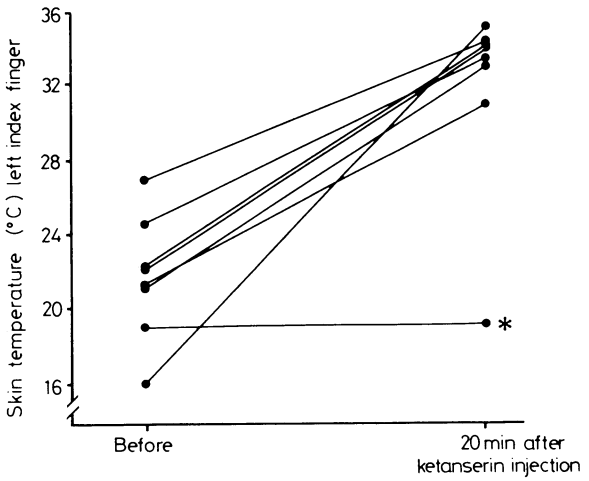


FIG 3—Digital skin temperature before and 20 minutes after intravenous injection of 10 mg ketanserin in eight patients with vasospastic disorders.
*Patient (case 6) with no measurable effect from 10 mg ketanserin.

Mean skin temperature of the left index finger (measured in eight patients) increased significantly from 21·8±1·2°C before treatment to 31·8±1·9°C 20 minutes after the injection (fig 3; $p<0·001$). The injection of saline had no effect on either the recorded pulse volume or temperature. The Brachial blood pressure was not significantly influenced by ketanserin. The only adverse effects of ketanserin were a transient sedation and dizziness in four patients.

## Discussion

The digital pulse volume recordings, which directly reflect finger blood flow, increased significantly after intravenous injection of ketanserin. This improvement in circulation was also shown by the increase in digital skin temperature. The increase in amplitude of the pulse volume tracings showed that the dominant effect was on the precapillary resistance vessels. The relatively large negative pulse volume derivative (dPVR/dt; fig 1) indicated an increased capillary run-off and suggested that there was also some dilatation of the capacitance vessels. In this respect the results agree with the findings of Wenting *et al*,[7] who studied the effects of ketanserin in patients with essential hypertension.

That ketanserin dilates constricted finger vessels is interesting, since the serotonin antagonist methysergide may induce arterial spasm in cold, pulseless limbs.[8] Ketanserin, however, is a pure 5-hydroxytryptamine$_2$ antagonist, whereas methysergide also has an intrinsic serotonin agonistic effect on blood vessels.[9]

Ketanserin antagonises both the vasoconstricting and platelet-aggregating effects of serotonin.[10] This dual effect is of particular interest in Raynaud's phenomenon, because in addition to the digital vasospasm[11] increased platelet aggregation has been reported in these patients.

Several vasoactive drugs have been tried in Raynaud's phenomenon but their use is limited by side effects[12] and the relative complexity of regional intravenous and intra-arterial injections of such drugs. In contrast, ketanserin is well absorbed from the gastrointestinal tract and appears to have few side effects.[13] Oral administration of ketanserin thus offers a new approach in the treatment of Raynaud's disease. Ketanserin has only recently been released for clinical evaluation and experience is therefore limited. Our clinical impression, however, is that tablets of ketanserin (20 mg twice daily) not only offer considerable symptomatic relief but also promote healing of digital ulcers in these patients.

## References

[1] Coffman JD, Davies T. Vasospastic disorders: a review. *Prog Cardiovasc Dis* 1975;**18**:123-46.
[2] Halperin JL, Coffman JD. Pathophysiology of Raynaud's disease. *Arch Intern Med* 1979;**139**:89-92.
[3] Halpern A, Kuhn PH, Shaftel HE, *et al.* Raynaud's phenomenon and serotonin. *Angiology* 1960;**11**:151-67.
[4] Allen EV, Brown GE. Raynaud's disease: a critical review of minor requisites for diagnosis. *Am J Med Sci* 1932;**183**:187-200.
[5] Stranden E, Grip A. Fotopletysmografi. *Tidsskr Nor Laegeforen* 1981;**101**, 17-18:1071-3.
[6] Hertzmann AB. Photoelectric plethysmography of the fingers and toes in man. *Proc Soc Exp Biol Med* 1937;**37**:529-34.
[7] Wenting GJ, Man in't Veld AJ, Woittiez AJ, Boomsma F, Schalekamp MADH. Treatment of hypertension with ketanserin, a new selective 5-$HT_2$ receptor antagonist. *Br Med J* 1982;**284**:537-9.
[8] Wintrobe MM, Thorn GW, Adams RD, *et al. Principles of internal medicine.* 6th ed. New York: McGraw-Hill, 1970.
[9] Van Nueten JM, Janssen PAJ, Ridder WD, Vanhouette PM. Interaction between 5-hydroxytryptamine and other vasoconstrictor substances in the isolated femoral artery of the rabbit; effect of ketanserin (R 41 468). *Eur J Pharmacol* 1982;**77**:281-7.
[10] Janssen PAJ. The pharmacology of specific, pure and potent serotonin 5-$HT_2$ or $S_2$-antagonists. In: Yoshida H, Hagihara Y, Ebashi S, eds. *Advances of pharmacology and therapeutics II.* Vol 4. Oxford, New York: Pergamon Press, 1982:21-33.
[11] Zahavi J, Hamilton WAP, O'Reilly MJG, Leyton J, Cotton LT, Kakkar VV. Plasma exchange and platelet function in Raynaud's phenomenon. *Thromb Res* 1980;**19**:77-88.
[12] Blunt RJ, Porter JM. Raynaud syndrome. *Semin Arthritis Rheum* 1981; **10**:282-308.
[13] De Cree J, Leempoels J, Geukens H, De Cock W, Verhagen H. The antihypertensive effects of ketanserin (R 41468), a novel 5-hydroxytryptamine-blocking agent, in patients with essential hypertension. *Cli Sci* 1981;**61**:473-6S.


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# Pericapillary fibrin in the ulcer-bearing skin of the leg: the cause of lipodermatosclerosis and venous ulceration

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## Abstract

**Forty-one biopsy specimens, taken from the ulcer-bearing skin of 41 legs of 21 patients attending the varicose vein clinic, were selectively stained for fibrin with phosphotungstic acid haematoxylin before being blindly assessed. Layers of fibrin were found surrounding the dermal capillaries in all 26 legs with lipodermatosclerosis. None of the specimens from the 15 legs with clinically normal skin contained fibrin. There was also an increased number of dermal capillaries cut in cross section per high powered field in 24 of the 26 legs with lipodermatosclerosis compared with two of the 15 legs with normal skin ($p < 0.001$). The mean reduction in foot vein pressure during exercise was significantly less in the 26 limbs with pericapillary fibrin than in the other 15 limbs ($p < 10^{-6}$). Lipodermatosclerosis is synonymous with pericapillary fibrin deposition and is associated with, and probably secondary to, both a persistently raised venous pressure and an increase in the size of the dermal capillary bed. This extravascular deposition of fibrin probably stimulates tissue fibrosis and blocks the diffusion of oxygen to the overlying epidermis, producing cellular death and venous ulceration.**


## Introduction

The mechanism by which venous disorders of the leg produce ulceration around the ankle is unknown. Ulceration is the final event in a well-recognised series of changes in the skin and subcutaneous tissues. The first changes are cutaneous pigmentation, mild ankle oedema, and the appearance of dilated subdermal venules. Later the skin and subcutaneous fat becomes thickened and hard. Since the tissues are often red and tender they are mistakenly thought to be infected or to be the site of superficial thrombophlebitis. At this stage minor trauma will cause an ulcer. If ulceration does not occur the skin and fat contract and the patient develops a tight narrow gaiter of hard skin. We prefer to call this whole process "lipodermatosclerosis" rather than give each clinical phase a separate name.

In a series of experiments designed to elucidate the underlying cause of these changes we have shown that legs with poor calf pump function, as shown by the failure of exercise to reduce foot vein pressure, have an increased number of capillary loops within the ulcer-bearing skin.[1] Confirmation that this was a causal relation was obtained from an animal study in which an increase in the venous pressure produced a similar increase in the size of the capillary bed of the calf skin.[2]

Increasing the capillary pressure opens the intercellular endothelial pores and increases capillary permeability.[3 4] Studies in animals showed that the high intraluminal venous pressure and increased endothelial surface area available for exchange did not change the rate at which albumin and sodium escaped from the vascular compartment into the subcutaneous tissue fluid, but fibrinogen, a much larger molecule, accumulated significantly faster in the tissue fluid around the enlarged capillary bed.[2]

The object of this study was to determine whether chronic venous hypertension and lipodermatosclerosis were associated with the accumulation of fibrinogen-fibrin in the perivascular interstitial spaces of human limbs.

## Patients and methods

We studied 42 legs of 21 patients (10 men and 11 women) without venous ulceration who were attending our varicose vein clinic. The limbs were examined for evidence of superficial, communicating, and deep-vein incompetence. The presence of liposclerosis was noted. Foot vein pressure during rest and exercise was measured successfully in 41 of the 42 legs. The foot veins of one limb could not be cannulated so this limb was excluded from the study. The method of pressure measurement has been described in detail elsewhere.[5] The results for each leg were obtained by expressing the fall in pressure (mm Hg) as a percentage of the resting pressure. Bipedal phlebograms were obtained from all patients using the method described by Lea Thomas.[6]

The results of the clinical examination and phlebography were combined to classify all limbs into one of four categories, each

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