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Ketanserin in reflex sympathetic dystrophy. A double-blind placebo controlled cross-over trial

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Summary Ketanserin, a selective S2 serotonergic antagonist, was assessed against placebo in a double-blind cross-over study of 16 patients with chronic peripheral burning pain. Nine of these had signs of reflex sympathetic dystrophy (RSD). All patients underwent 4 intravenous regional treatments, 2 with ketanserin (10 mg for upper limb pain, 20 mg for lower limb pain) and 2 with placebo. In those patients with RSD ketanserin and not placebo provided significant ($P < 0.05$) sustained pain relief as assessed by linear analogue scales. In patients who did not fulfil the criteria for RSD no significant relief was seen with placebo or ketanserin.

Following tourniquet release, drowsiness, shakiness and faintness were reported at a higher ($P < 0.05$) frequency after ketanserin than after placebo. All side effects were mild and transient, and no changes occurred in heart rate or blood pressure following ketanserin that were significantly different from those seen following placebo.

A role for serotonin in the pathogenesis of RSD is proposed.

Key words: Ketanserin; Reflex sympathetic dystrophy

Introduction

The reflex sympathetic dystrophy syndrome (RSD) characteristically consists of sustained burning pain, vasomotor disturbances, functional disability and trophic changes in the absence of major nerve injury [12]. The syndrome can follow any trauma, particularly at the wrist or ankle, but the initiating event may be mild or unknown [3,12–14]. Sympathectomy has proved an effective therapy, particularly when performed early in the evolution of the condition, but repeated blocks are often needed and may fail if treatment is delayed [12].

Initial reports of the use of the serotonin type 2 receptor antagonist ketanserin by i.v. bolus suggested it to be of considerable benefit in RSD [8], however, this was not confirmed in a controlled investigation [4]. Ketanserin administered using an intravenous regional technique appeared to provide sustained pain relief in patients suffering from RSD in an open unblinded study conducted in this unit (unpublished observation).

A prospective randomised double-blind cross-over trial of ketanserin against placebo was undertaken in order to verify this finding.

Methods

Patient selection

Sixteen patients with severe peripheral burning pain gave written consent to the study as approved by the hospital ethical committee. Patient details are presented in Table I. Prior to the start of the investigation patients were divided into 2 diagnostic groups on the basis of clinical examina-

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TABLE I

DETAILS OF PATIENTS IN TRIAL

	Age (years)	Sex	Treatment group	Diagnostic group	Duration symptoms	Previous treatment
1	65	F	Y	Unknown	5 years	Nil
2	38	F	X	Raynaud's	8 years	Plasmapheresis, guanethidine
3	55	M	X	Neuropathy	2 years	Analgesics
4	46	F	Y	RSD	3 years	Analgesics, antidepressants
5	66	M	Y	Ischaemic	2 years	Analgesics, vascular surgery
6	72	F	X	RSD	1 year	Analgesics
7	79	F	Y	Neuropathy	4 years	Analgesics
8	54	F	Y	RSD	18 months	Analgesics
9	64	M	Y	RSD	6 years	Guanethidine
10	56	M	X	Unknown	6 years	Analgesics
11	71	M	X	Unknown	14 years	Analgesics
12	37	F	X	RSD	4 years	Analgesics
13	66	F	Y	RSD	3 years	Analgesics
14	61	F	Y	RSD	5 months	Nil
15	54	F	Y	RSD	2 months	Nil
16	55	F	Y	RSD	4 months	Nil

tion. Those with features of RSD (vasospasm, oedema and trophic changes) in addition to constant burning pain were placed in the RSD group and those lacking these features into the non-RSD group. Each patient was then randomly assigned to treatment group X or Y. Patients in group X (n = 6) received 2 ketanserin treatments followed by 2 placebo treatments, and those in group Y (n = 10) 2 placebo treatments followed by ketanserin treatments.

Drug administration

Treatments were given at weekly intervals on a double-blind basis in a temperature stabilised room. Placebo and ketanserin (Janssen Pharmaceuticals) were buffered to pH 4 and made up to 30 ml with isotonic saline. Ketanserin (10 mg for arm pain, 20 mg for leg pain) or placebo was injected via a 23-gauge indwelling cannula in the dorsum of the hand or foot immediately after limb exsanguination and isolation by pneumatic tourniquet. Limb isolation was maintained for 15 min using tourniquet pressures exceeding systolic by 100 mm Hg for a lower limb and 50 mm Hg for an upper limb.

Assessments

Blood pressure and heart rate (by automatic oscillotonometry on non-treatment arm) and bilateral digit temperature (thermocouple) were measured before treatment, during limb isolation and at set times following cuff release. Pain was assessed by the patient, using a 10 cm visual analogue scale, at noon on each day of the week prior to the start of drug administration and in a similar manner for the subsequent 4 weeks. Side effects following cuff release were assessed by the

TABLE II

INCIDENCE OF SIDE EFFECTS (%) ON QUESTIONING

Side effect	Incidence (%)	
	Placebo	Ketanserin
Pain on injection	61	62
Headache	18	14
Injection site soreness	39	28
Drowsiness	4	38 ($P < 0.001$)
Faintness	0	17 ($P < 0.025$)
Shakiness	0	10 ($P < 0.05$)
Palpitations	0	3
Visual disturbance	0	3

patients' response to questions read by the assessor from a check list (see Table II).

Blood samples were taken via an indwelling cannula in the non-treatment arm before and during limb isolation and at 5, 10, 15, 30, and 60 min following cuff release. Serum ketanserin levels were measured by high performance liquid chromatography [9] (Janssen Pharmaceuticals)

Statistical methods

Mean pain scores for each patient for each week of the study were calculated and these values used for subsequent analysis. Paired t tests were used to assess changes in pain scores, blood pressure, heart rate and digital temperature. The incidence of side effects resulting from administration of placebo and ketanserin was analysed using the chi-square test.

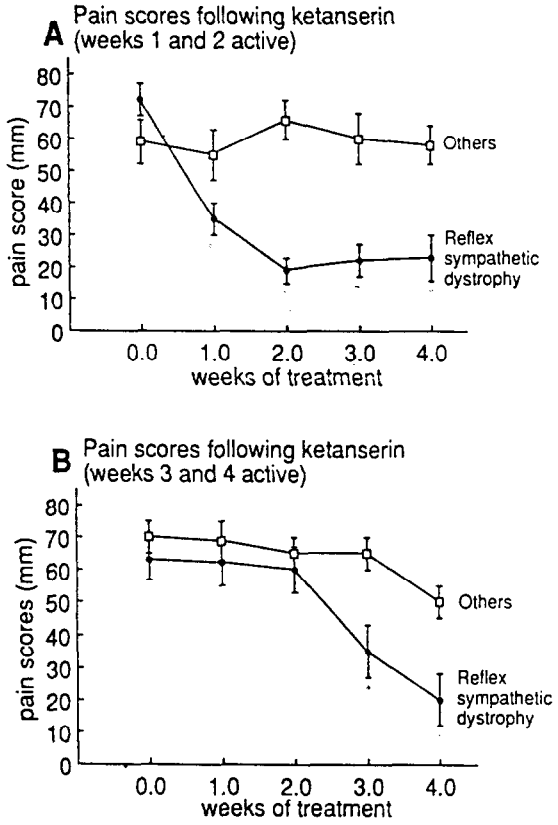

Fig. 1. Analgesic response to ketanserin and placebo. Linear analogue pain scores for patients with reflex sympathetic dystrophy or other causes for peripheral burning pain. Results expressed as mean (±S.E.M.). A: patients receiving ketanserin on weeks 1 and 2. B: patients receiving ketanserin on weeks 3 and 4. Values marked ★ differ significantly from pretreatment values ($P < 0.05$).

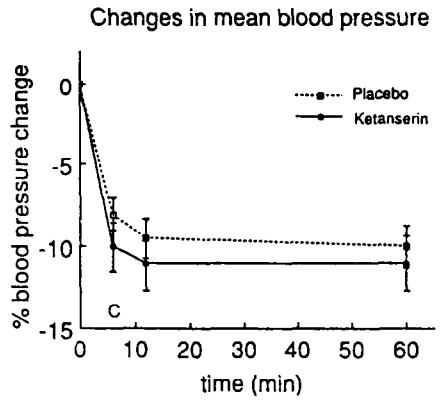

Fig. 2. Change in mean blood pressure following ketanserin and placebo. Results expressed as mean (±S.E.M.) % change from resting mean blood pressure. Tourniquet released at C. All measurements differ significantly from pretreatment values ($P < 0.001$).

Results

Pain scores

A significant decrease in mean pain score was seen during active treatment weeks only in those patients in the RSD group ($P < 0.05$). The beneficial effect continued into the placebo weeks in patients who received ketanserin first. Patients in the non-RSD group showed no significant change in mean pain score during placebo or ketanserin weeks (Fig. 1).

Cardiovascular stability

A significant ($P < 0.001$) decrease in mean blood pressure after tourniquet release occurred following both placebo and ketanserin treatments. This was not significantly greater following ketanserin (Fig. 2). No significant changes were seen in heart rate.

Limb temperatures

Treatment limb. Digital temperature fell during arterial occlusion and rose following tourniquet release. The increase following ketanserin was in-

significantly greater than that following placebo (Fig. 3).

Non-treatment limb. Following ketanserin digital temperature increased. This increase was significantly greater than that occurring following placebo ($P < 0.05$) (Fig. 3).

Side effects

Feelings of faintness, shakiness and drowsiness occurred significantly more often with ketanserin. Pain on injection and other side effects were no more frequent than with placebo (Table II). All side effects passed within 1 h.

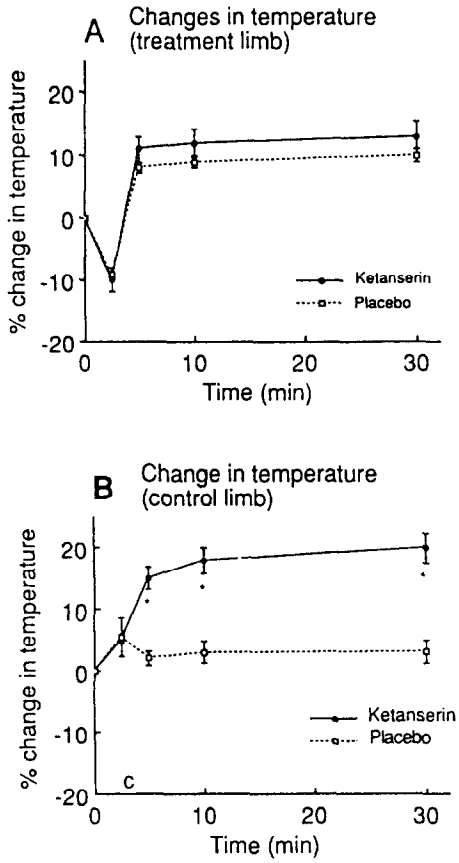

Fig. 3. Change in digital temperature following ketanserin and placebo. A: treatment arm. B: non-treatment arm. Results expressed as mean (±S.E.M.) % change from resting temperature. Tourniquet released at C. Values marked ★ differ significantly from placebo ($P < 0.001$).

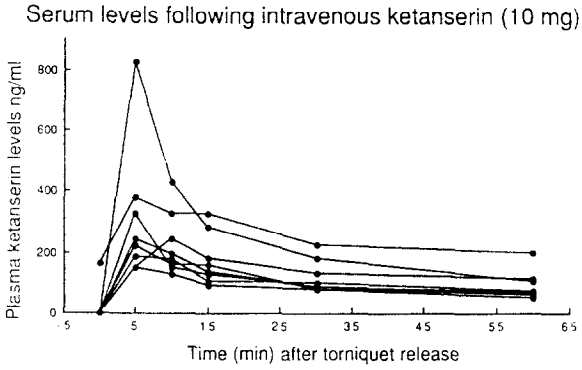

Fig. 4. Serum ketanserin levels in 8 patients before and after tourniquet release at time 0.

Ketanserin levels

Ketanserin assay was completed in 8 patients (Fig. 4). One patient showed ineffective cuff isolation, as demonstrated by detectable systemic ketanserin levels before cuff release.

Discussion

The results demonstrate that the selective serotonin type 2 receptor antagonist ketanserin [6] and not placebo produces a sustained improvement in the pain component of the reflex sympathetic dystrophy syndrome (RSD). Patients admitted to the trial with pain, but lacking the clinical features of RSD, did not respond to ketanserin with the exception of the one patient suffering from Raynaud's phenomenon. Patients in the RSD group not achieving total pain relief by the end of the trial were offered two further treatments with ketanserin. All accepted and pain was totally abolished in all but one of these (patient 9).

The aetiology of RSD is uncertain, although evidence for peripheral and central mechanisms has been presented [3,12–14]. Increased sympathetic tone and a relative excess of the neurotransmitter noradrenaline have been implicated in RSD. The therapeutic success of sympathectomy and peripheral adrenergic nerve blocks using guanethidine appears to support these hypotheses [12,13], although some patients fail to respond to these treatments.

A large number of substances, including serotonin, play a significant role in autonomic transmission or its modulation [5]. In rat isolated caudal artery serotonin greatly amplifies the vasoconstrictor response to sympathetic stimulation or application of noradrenaline [7], and in rabbit femoral artery serotonin is highly synergistic with histamine, angiotensin II and prostaglandin F2α [6]. These effects, which are antagonised by ketanserin, appear to be mediated via S2 receptors.

Low concentrations of serotonin are capable of causing prolonged pain when applied to human experimental blisters [1]. In isolated human hand arteries of less than 1 mm diameter, serotonin has constrictor activity comparable with that of sympathomimetic agents. This is antagonised by ketanserin and not phentolamine, suggesting that the effect is via serotonergic rather than alpha-adrenergic receptors. There is a component of irreversibility to this blockade, and exposure of the vessels to ketanserin for 40 min produces antagonism to serotonin which is resistant to repeated washing [2]. A similar mechanism may account for the prolonged beneficial effect seen in our RSD patients, since the method of administration used involves the short-term exposure of limb blood vessels to high local ketanserin concentrations. It may also explain the lack of response in a controlled study where i.v. ketanserin without limb isolation was used [4].

Plasma levels reached in the present study are of the same order as those reported following bolus doses of 0.15 mg/kg [9], and the increased temperature in the non-treatment arm confirms a systemic cutaneous vasodilator effect. The alpha-adrenoceptor blocking properties of ketanserin have been assessed by its ability to attenuate the hypertensive response to phenylephrine [15] and methoxamine [9] in volunteers. Evidence of alpha blockade following intravenous ketanserin has been detected at plasma levels of 85–90 μg/l [10], and with chronic oral administration at concentrations as low as 33.7 ng/ml [15]. A systemic alpha-adrenolytic effect of short duration would therefore be expected in the present study. Ketanserin does not influence the response of human vascular smooth muscle to noradrenaline in vitro [2], although blockade of peripheral vascular alpha receptors may contribute to the antihypertensive action of ketanserin in vivo [10].

A systemic alpha-adrenolytic action of ketanserin is unlikely to account for the prolonged analgesia ketanserin provides, but a local mechanism of action mediated via alpha receptors could be involved in view of the technique used. In RSD an increase in local serotonin levels, or an increased sensitivity to serotonin, could result in pain and vasoconstriction both by a direct action and by amplification of the response to sympathetic stimulation and endogenous vasoconstrictors. The hypothesis that serotonin has a role to play in RSD is supported by the demonstration of a sustained beneficial effect of ketanserin in this condition.

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