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Original Articles

A Double-Blind Controlled Trial of Salmon Calcitonin in Pain due to Malignancy

A. C. Hindley, E. B. Hill*, M. J. Leyland, and Anne E. Wiles**

Department of Clinical Haematology, East Birmingham Hospital, Bordesley Green East, Birmingham, Great Britain

Summary. *Thirty-two patients with established malignancy and associated pain participated in a randomised double-blind controlled trial. They received salmon calcitonin SC 200 IU or matching placebo 6-hourly for 48 h and were assessed by using a combination of a 20-point visual analogue scale (VAS), a 4-point physician's global pain scale, and ranking of the co-administered analgesics into 20 grades of potency. Twenty-five patients (13 calcitonin, 12 placebo) were evaluated. Seven patients (4 calcitonin, 3 placebo) were excluded either because the initial pain score was ≤ 5 on the VAS, or because there were insufficient data (due to death occurring within the first week of the study or, in one patient, blindness preventing completion of the VAS).*

One week after commencing therapy there was improvement or marked improvement of pain in significantly more patients in the calcitonin group (5/13) than in the placebo group (0/12) (Fisher's exact two-tailed probability test, P = 0.0484). At the end of the second week three patients in the calcitonin group were still showing marked improvement.

Introduction

Calcitonin is the most widely recognised treatment for pain in Paget's disease [4, 6]. Recently there have been reports of its effectiveness in the treatment of bone pain in malignancy [1, 2, 5]. However, these studies were not only uncontrolled, but also did not take into account the effects of concurrent anti-tumour therapy or analgesia. Furthermore, calcitonin was administered for a prolonged period of time, on a daily basis for up to 6 weeks.

In a single open pilot study four of five patients with confirmed malignancy showed relief of their pain following a regimen of 200 IU salmon calcitonin 6-hourly for 48 h. The length of pain relief varied from 1–2 weeks in two patients to several weeks in the other two. All patients were normocalcaemic and no gross effect on their serum calcium was noted. A prospective double-blind placebo-controlled trial using the above regimen was therefore set up to evaluate these earlier findings.

Materials and Methods

Thirty-two patients entered the trial; 27 were in two homes for the terminally ill and five in a district general hospital. All were assessed clinically and had pain due to malignancy, though not necessarily due to bone involvement. Patients with a prognosis of less than 1 month or who had received active therapy within the last 3 weeks were excluded. The primary diagnosis and cause of pain in each patient are shown in Table 1.

The study was double-blind and placebo-controlled; patients were allocated in random order to receive either salmon calcitonin (Calsynar, Armour Pharmaceutial Co Ltd Great Britain), 200 IU or matching placebo (1 ml saline acetate diluent) 6-hourly for 48 h.

In addition, all patients received narcotic and/or anti-inflammatory drugs according to the practice of the unit concerned.

For the purposes of analysis the analgesic regimens were formalized and graded 1–20 in terms of potency. This consisted of diamorphine IM in a dose ranging from 5 mg 8-hourly to 180 mg 4-hourly in 14 stages in the case of one hospice and the District General Hospital. The other hospice used morphine and cocaine elixir BPC in doses ranging from 5 ml 8-hourly to 20 ml 4-hourly in nine stages, with two additional stages consisting of diamorphine 10 mg or 20 mg with chlorpromazine 50 mg IM 4-hourly. Phenylbutazone 100 mg 8-hourly was added if the pain was thought to be due to bony metastases.

Following baseline assessment and treatment observations were continued for 1 month or until death. Pain was assessed by the patients, daily for 14 days and then at weekly intervals, using a 20-point visual analogue rating scale (VAS) described by Huskisson [3].

Each week pain was assessed by the investigators using a global 4-point scale. Forty-eight hours after the start of treatment, an attempt was made to reduce analgesia in patients showing a reduction in their pain scores, in a predetermined step-wise manner.

The response to therapy in individual patients was assessed at weeks 1 and 2 in accordance with the following definitions:

'Much improvement': Decrease of ≥ 10 grades on the VAS *and* a decrease of at least one grade in the physician's global pain score *and* no more than one point rise in analgesic ranking

'Improvement': As above, but decrease of grades 5–9 inclusive in VAS

'Worse': Increase of grades 5–9 inclusive on VAS *and* increase of at least one grade in physician's global pain score

'Much worse': As above but an increase of ≥ 10 grades in VAS.

Reprint requests should be addressed to M. J. Leyland

* Medical officer to Warren Pearl Nursing Home

** Medical statistician

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Table 1. Diagnosis and cause of pain in 25 patients evaluated

Treatment	Patient no.	Primary diagnosis	Cause of pain	Bone involvement
Placebo	1	Maxillary antral carcinoma	Mucosal and bony erosion	+
	3	Mammary carcinoma	Pathological fracture	+
	8	Gastric carcinoma	Liver metastases	
	9	Uterine carcinoma	Mucosal ulceration	
	10	Rectal carcinoma	Soft tissue	
	11	Prostatic carcinoma	Bone metastases	+
	16	Bronchial carcinoma	Bone metastases	+
	18	Unknown primary	Bone metastases	+
	19	Renal carcinoma	Bone metastases	+
	21	Rectal carcinoma	Nerve root	
	25	Multiple myeloma	Bone involvement	+
	29	Mammary carcinoma	Bone metastases	+
Calcitonin	2	Rectal carcinoma	Nerve root	
	5	Cervical carcinoma	Nerve root	
	6	Rectal carcinoma	Soft tissue	
	7	Multiple myeloma	Bone involvement	+
	13	Mammary carcinoma	Pathological fracture	+
	14	Colonic carcinoma	Liver metastases	
	15	Renal carcinoma	Bone metastases	+
	20	Soft tissue sarcoma	Soft tissue/nerve root	
	23	Prostatic carcinoma	Bone metastases	+
	24	Unknown primary	Pathological fracture	+
	26	Mammary carcinoma	Bone metastases	+
	33	Mammary carcinoma	Bone metastases	+
	39	Multiple myeloma	Pathological fracture	+

Results

Seven patients in all were excluded from the full analysis (four calcitonin and three placebo) because of insufficient data, due to death in the first week in three cases (one calcitonin, two placebo), and to inability to complete the VAS in one calcitonin patient who was blind. The three other exclusions (two calcitonin and one placebo) were made because the patients' initial pain was very mild (VAS $\leqslant$ 5).

Table 2 gives details of the visual analogue score, the verbal ranking, and analgesic ranking initially and at the end of weeks 1 and 2. In the case of the VAS and analgesic ranking the values shown represent the median of days 5, 6, and 7 for week 1 and days 12, 13, and 14 for week 2. Nausea and vomiting were the only adverse effects noted, being significantly more severe on day 1 in the calcitonin group ($P < 0.05$) and occurring in 8/17 patients treated. Anti-emetics were given if required and none of the patients had sufficient toxicity for the drug to be withdrawn.

Analysis of the three parameters separately showed that 8/13 patients in the calcitonin group improved on the VAS at week 1, compared with 2/12 in the placebo group. However, this difference is not statistically significant ($P = 0.057$). Similarly, in terms of verbal ranking 7/13 calcitonin patients improved compared with 2/12 in the placebo group, which is again not statistically significant ($P = 0.1266$). There was also no significant difference in the numbers of patients who increased their analgesic level by more than one step (4/13 calcitonin, 6/12 placebo). However, when the composite definitions of response are applied the distribution of responses in the two groups is as shown in Table 3. There were 4/13 patients in the calcitonin group showing much improvement and a further patient showing improvement at the end of week 1, as against 0/12 improvements in the placebo group ($P = 0.0484$). At week 2 there were three patients in the calcitonin group who continued to show much improvement. It is interesting to note that all four patients showing much improvement in the calcitonin group at week 1 had bony metastases.

Discussion

The management of pain due to malignancy can be difficult, particularly in active patients who find the side-effects of narcotic analgesia unacceptable.

This double-blind placebo-controlled study suggests that in some patients calcitonin is effective in the treatment of pain associated with malignancy. The number of patients in each group is small, but stringent and clinically meaningful definitions of response have been applied. Significantly more patients experienced a reduction in the severity of their pain in the calcitonin group at week 1 (5/13) than in the placebo group (0/12) ($P = 0.0484$).

At the end of the second week three patients who had received calcitonin were still in the much improved group. Indeed, these three patients continued to show a sustained response for several weeks after the study was discontinued.

If the individual components of the definitions of response are considered separately the same trend is found, but possibly due to the small numbers involved does not attain statistical significance.

It is of interest that all four patients who showed much improvement in the calcitonin group at week 1 had bony

Table 2. Scores and analgesic rankings of calcitonin and placebo groups before the trial and after weeks 1 and 2

Patient	VAS			Global pain score			Analgesic ranking		
	Initial	Week 1	Week 2	Initial	Week 1	Week 2	Initial	Week 1	Week 2
Placebo group									
1	7	10	9	3	3	3	7	8	8
3	9	6	4	3	3	3	5	9	9
8	11	14	–	4	3	–	5	5	–
9	20	19	$9^1/_2$	4	4	1	0	3	2
10	9	15	$10^1/_2$	3	4	4	0	3	3
11	9	3	9	3	3	2	2	4	1
16	8	10	9	2	3	4	4	6	6
18	15	16	–	4	2	–	6	4	4
19	7	10	18	2	4	3	10	9	9
21	16	$14^1/_2$	–	4	4	–	12	18	–
25	15	$6^1/_2$	12	3	3	2	0	0	0
29	11	7	9	3	3	4	4	5	5
Calcitonin group									
2	8	3	5	3	4	–	4	4	7
5	16	9	9	4	3	3	3	4	6
6	6	10	$12^1/_2$	4	4	3	1	3	3
7	12	11	–	3	1	–	7	7	9
13	20	17	–	4	4	4	9	10	–
14	11	5	–	2	2	–	3	1	–
15	9	16	0	4	1	–	0	8	9
20	14	10	3	4	4	1	8	6	6
23	18	6	–	3	3	–	0	2	–
24	15	3	4	4	2	4	1	2	3
26	18	6	6	4	3	3	4	5	5
33	19	1	2	4	1	4	0	1	0
39	17	3	7	4	2	3	0	0	0

Visual analogue score (VAS) values represent median of days 5, 6, and 7 for week 1 and days 12, 13, and 14 for week 2. Absent data at week 2 due to patient deaths

Table 3. Distribution of responses

	Week 1		Week 2	
	Calcitonin	Placebo	Calcitonin	Placebo
Much improvement	4	0	3	0
Improvement	1	0	0	0
Worse	0	1	0	1
Much Worse	0	0	0	0
		Missing	6	3
Proportion of responders:				
a) Week 1			Fisher's exact 2-tailed test of probability	
Much improvement	4/13	0/12	$p = 0.1130$	
Some improvement	5/13	0/12	$p = 0.0484$	
b) Week 2				
Much improvement	3/7	0/9	$p = 0.1250$	
Some improvement	0/7	0/9		

metastases. This may give some indication of the type of patient who may benefit from such therapy. Nevertheless, the mode of action of calcitonin in this condition is not clear and further studies are required not only to identify specific sub-groups of patients who may respond to therapy but also to define the optimum dose and mode of action in this situation.

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