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Papers

A Prospective, Randomised Double-blind Crossover Study to Examine the Efficacy of Strontium-89 in Pain Palliation in Patients with Advanced Prostate Cancer Metastatic to Bone

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The palliative efficacy of strontium-89 chloride has been evaluated in a prospective double-blind crossover study comparing it with stable strontium as placebo in 32 patients with prostate cancer metastatic to bone. Response was assessed 5 weeks after each treatment. 26 patients were evaluable. Complete pain relief was only reported following strontium-89 injection. Statistical comparison between placebo and strontium-89 showed clear evidence of a therapeutic response to strontium-89 compared with only a limited placebo effect ($P < 0.01$).
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INTRODUCTION

BONE PAIN is a common clinical problem in disseminated prostatic carcinoma which is often very difficult to control effectively [1]. Approximately 70% of patients respond to first-line hormone therapy [2] but the majority eventually escape hormonal control and develop pain secondary to progessive bone metastases. Pain limited to a single site usually benefits from local-field radiotherapy, but rapid dissemination of metastases often necessitates multiple single-field treatments, administered concurrently or sequentially [3].

Wide-field radiotherapy is an effective palliative treatment [4] but is associated with significant morbidity and recurrence of pain in a large number of patients treated. For many, therefore, the only available therapeutic option is the administration of escalating doses of narcotic analgesics, supplemented by radiotherapy.

Sclerotic bone metastases cause an intense osteoblastic reaction in adjacent bone; this is seen as intense increased uptake of technetium-99m MDP on radionuclide bone imaging. These sites of increased bone turnover might be expected to have a high affinity for strontium-89 which could, therefore, have therapeutic potential [5].

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The first report of the clinical use of strontium-89 was by Pecher [6] who suggested some analgesic response in a small series of patients with a variety of primary malignancies, including prostate cancer. Further reports [7, 8] confirmed this effect in two small series.

The first large series assessing the efficacy of strontium-89 was reported by Robinson's group [5, 9] who demonstrated response rates of the order of 75% in patients with prostate cancer. In this series a range of doses of 1.11–1.48 MBq/kg was used. A recent report has demonstrated strontium-89 to be a safe and effective therapy in patients with prostate cancer who had previously been treated with wide-field radiotherapy [10].

This study was designed to assess the contribution of the placebo response and of the chemical effect of carrier strontium to pain relief in patients treated with strontium-89.

MATERIALS AND METHODS

Patient population

32 patients (aged 64–79 years) from seven hospitals were studied; the study was approved by the ethics committees of the participating institutions and all trial patients gave appropriate written informed consent. All patients had prostate carcinoma metastatic to bone which had escaped control by conventional treatments (hormone manipulation, local radiotherapy or analgesics). Hormone therapy had not been altered in the preceding 3 months and accrual was only permitted if predicted life expectancy was at least 4 months. All patients had increasing requirements for narcotic analgesics.

Patients were not excluded on the basis of previous irradiation, although they were not included if currently receiving local external beam radiotherapy. Patients over the age of 80 and those unable to complete the forms were all excluded, as were patients with a Karnofsky index of less than 5.

Pretherapy assessment

Before the first injection, all patients underwent a complete physical examination at which sites of pain were recorded by the examining physician, with an assessment of mobility and Karnofsky status. A full blood count was obtained and a radionuclide bone image was obtained if one had not been performed within 4 weeks of administration. In addition, all patients kept a pain and analgesic diary using previously described techniques [10]. These data were used as baseline for subsequent post injection evaluations.

Treatment schedule

Two treatments were compared: stable strontium (natural mixture of isotopes, predominantly Strontium-88) chloride (50 mg) spiked with a tracer dose of 3.7 MBq of strontium-85; and strontium-89 chloride (150 MBq) containing stable strontium chloride (50 mg) spiked with a tracer dose of 3.7 MBq of strontium-85.

Both the strontium-89 and the placebo were spiked with strontium-85 to mask the Bremsstrahlung ("white" radiation) from the strontium-89, which could have lead to inadvertent breaking of the trial code.

The radiopharmaceutical was administered by slow peripheral intravenous injection in the antecubital fossa. The radiopharmaceuticals were supplied in coded vials by Amersham International, who, as the central statistical office, were responsible for randomisation utilising random number tables.

Patients in the trial were randomly assigned to receive one or other of the two injections; after follow-up examination at 5 weeks the second injection was normally administered at 6 weeks.

Patients who had become pain-free after the first injection or whose clinical condition had deteriorated to the extent that they could not continue in the trial did not receive the second injection.

The treatment groups were comparable regarding performance status, analgesic requirement and disease extent as assessed by radionuclide bone imaging.

Post-therapy evaluation

Response was evaluated 5 weeks after each injection using a numerical weighting system. This incorporated all the clinical data collected and provided a semiquantitative assessment of individual response. Sites of pain were scored independently according to a reference chart and particular attention was given to analgesic intake. The physician's records were corroborated by the patients' diaries and a full blood count was obtained at each visit.

The scoring system is outlined in Table 1, which includes the numerical definition of overall response. To be graded 5 the patient effectively became pain-free and returned to full mobility.

If, at 5 weeks, the patient was pain-free, the second injection was not administered, but follow-up continued. If measurable pain persisted, the second vial was administered. Follow-up was as for the first administration and response was again assessed 5 weeks after injection.

Patients were considered to be non-evaluable if they died prior to assessment, were lost to follow-up, had additional treatment or if the code was broken.

Statistical analysis

For statistical analysis, the results of the treatment response assessments were considered as two sets of data. Assessments

Table 1. Scoring in post-therapy evaluation

General condition	
Deteriorated	−1
Unchanged	0
Some improvement	+1
Definitely better	+2
Mobility	
More restricted	−1
Essentially unchanged	0
Less restricted	+1
Analgesics	
Quantity increased	−1
Essentially unchanged	0
Quantity decreased by 20–45%	+1
Quantity decreased by 50–80%	+2
Analgesics virtually discontinued	+3
Pain analysis	
At least 1 point increase in the majority of affected sites	−2
About 1 point increase in some sites	−1
No change in most sites	0
About 1 point decrease in some sites	+1
At least 1 point decrease in the majority of affected sites	+2

Overall assessment. Based upon the summation of the four assessments, the patient is assigned to one of the following five response categories.

	Guideline total of scores
1. Deteriorated	Negative
2. No significant change	−1/0/+1
3. Some improvement	+1/2/3
4. Substantial improvement	+4/5/6
5. Dramatic improvement	+7/8

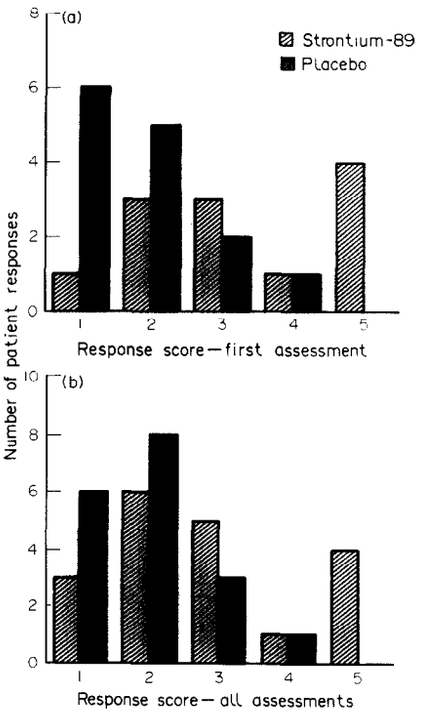

Fig. 1. Clinical response (a) for first assessment and (b) for all assessments.

Table 2. Reasons for not giving second treatment

Reason	First treatment	
	Placebo	Strontium-89
Pain adequately controlled following first treatment	1	4
Too ill to continue in trial	3	-
Platelet levels depressed after first treatment	1	1

made after the first treatment may be considered free from bias as treatments were randomly allocated and assessed blind. Assessments made after both treatments are free of systematic bias but are not statistically independent as the effects of the first treatment may have persisted and influenced the second assessment.

Both sets of data were analysed with *t* tests. This analysis is unbiased, but can be criticised on the grounds that it makes arbitrary assumptions regarding the quantitative differences between the gradings. Therefore the data were also analysed as ordered categorical response variables [11, 12], a method not open to this criticism.

Haematological toxicity was assessed by comparing the fall in platelets following injection with placebo and strontium-89 and after both injections by *t* tests.

RESULTS

Clinical reponse

32 patients received the first injection, of whom 26 were evaluable at 5 weeks. 10 patients did not proceed to the second injection (Table 2); of these 5 had received placebo and 5 strontium-89. 16 patients, therefore, received the second injection, of whom 11 were evaluable at 5 weeks. Table 3 documents all unassessable patients. The responses of these patients are presented in Fig. 1.

Figure 1(a) reviews the response as assessed at 5 weeks after the first injection, comparing the levels of response between placebo and strontium-89. Figure 1(b) reviews responses after both injections, comparing placebo and strontium-89 in a total of 37 responses: 26 after the first injection and 11 after the second.

Treatment toxicity

No immediate adverse reaction to either injection was noted. Complete haematological data were available in 15 patients who received placebo as the first injection, in 12 who received strontium-89 as the first injection and in 13 who received both injections. These data are plotted in Fig. 2.

Table 3. Reasons for declaring patient unassessable

Reason	Placebo		Strontium-89	
	1st	2nd	1st	2nd
Died or too ill to assess	3	-	2	-
Change in other therapy during assessment period	-	-	1	-
Code broken	-	2	-	1
Other reason	-	1	-	1

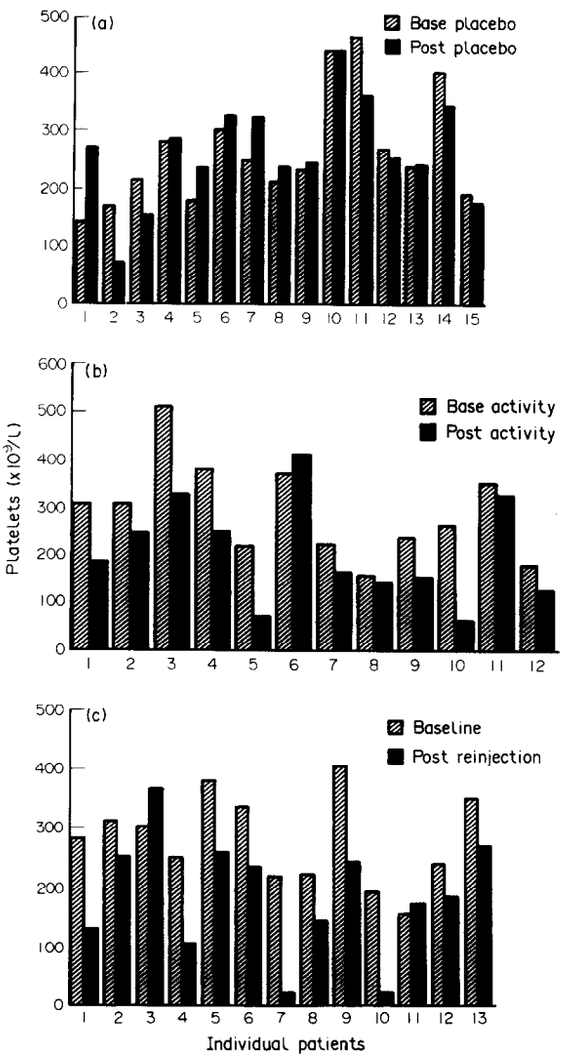

Fig. 2. Platelet levels compared between baseline values and 5 weeks after the first injection (a) where that injection was placebo and (b) where that injection was strontium-89; and (c) after the second injection.

In 3 patients platelet levels fell to 50–75 × 10^9/l (RTOG grade 2 toxicity) after the first injection [Figs 2(a) and (b)]. 1 of these patients had received stable strontium.

When the platelet count was assessed in patients who had received both injections, 2 patients showed RTOG grade 4 toxicity, with levels below 25 × 10^9/l [Fig. 2(c)]. Neither patient became symptomatic; 1 patient was not clinically evaluable.

The mean fall in platelets from baseline values in patients receiving strontium-89 as the first injection was 101 × 10^9/l ($P < 0.0001$). The mean fall from baseline values after both injections was 104 × 10^9/l ($P < 0.0001$). No significant change in platelet count was shown in patients who received placebo as the first injection.

Statistical analysis of response

The clinical results recorded in Fig. 1 compare overall numbers of responders of evaluable patients at each response level after the first treatment and after both treatments.

In the *t* test, strontium-89 was more effective than placebo if

the first assessment only was used ($P < 0.01$) and if both assessments were used ($P < 0.03$). Treating the data more rigourously, as categorical response variables, produced virtually identical conclusions.

DISCUSSION

The results show a significant difference between the clinical efficacy of strontium-89 and stable strontium. Only patients who had received strontium-89 became completely pain-free after the first injection. Patients who did not benefit were predominantly from the non-radioactive strontium group.

Whilst a measure of placebo response may be expected in a trial of this design, the statistical analysis of these data suggests that the limited placebo response observed cannot explain the therapeutic efficacy of strontium-89. Similarly, pain relief cannot be attributed to a chemical effect of ionic strontium.

No significant toxicity was recorded in either group after the first injection. Of the 2 patients who showed a significant fall in platelet count at the second follow-up period, one received strontium-89 as the first injection. This patient showed a progressive fall in platelets over the follow-up period, and did not proceed to the second injection. The second patient received placebo as the first injection and only showed a significant fall after the second, active therapy.

The only reported adverse effect following treatment with strontium-89 appeared to be myelosuppression, with a transient fall in platelets being recorded [5, 10], even in patients who have been heavily pretreated [13]. This appears to be maximal between 3 and 5 weeks after injection with satisfactory recovery thereafter. There are no reports in the literature of significant clinical toxicity occurring after treatment with strontium-89.

In patient populations that have been treated with strontium-89, particularly those with prostate cancer, it is often difficult to distinguish myelosuppression secondary to progressive disease from that due to treatment-related toxicity. Following strontium-89 therapy, the platelets appear to be the most sensitive cellular elements, with neither haemoglobin values nor white cell counts showing significant differences between the active and placebo groups.

The changes in platelet count documented in Fig. 2 show significant differences between the active and placebo groups. No significant change was observed following placebo in comparison with a mean reduction to 75% of baseline values after strontium-89. This decrease was not clinically significant and did not contribute to morbidity.

The number of patients showing a fall in platelet level to 70% or less of baseline is comparable in both treatment groups. Reductions below 30% of baseline were only observed in 2 patients following active strontium. 2 patients developed clinically significant toxicity 11 weeks after the first treatment, reflecting the combined effects of strontium toxicity and progressive marrow infiltration by tumour.

These data support the view that patients who have adequate platelet levels pretherapy are unlikely to suffer marrow toxicity after treatment with strontium-89 at this dose.

The limited clinical trials performed to date have been unblinded studies using a standard dose of strontium-89 usually administered according to body weight. The range of doses has varied from 0.7 to 3.0 MBq per kg, with 1.5–3.0 MBq/kg being claimed as effective. The dose of strontium-89 (150 MBq) used in this study falls within this recommended range. Experience with higher doses of strontium-89 has been reported using up to 800 MBq strontium-89 as a single dose [14]; however, this does not appear to confer additional symptomatic benefit.

We are aware of one other study comparing placebo and strontium-89 [15] which showed no symptomatic benefit in response to strontium-89. This discrepancy may be explained by major differences in trial design. The dose schedule used by Buchali and coworkers included fractionated doses of strontium-89 in conjunction with hormone therapy which did not fall within commonly used protocols. Our patient population was treated using a single agent and had not undergone any change of therapy, other than increasing analgesic administration, for 3 months preceding entry into the trial. The current trial data appear more appropriate for the evaluation of pain relief and placebo response.

The palliation of painful bone metastases remains a large component of clinical oncological practice. The introduction of strontium-89 offers considerable potential in the management of these distressing symptoms in this group of patients.

There is now clear evidence that strontium-89 is an effective palliative therapy for patients with prostate cancer who have advanced disease and also for patients who have previously received extensive radiotherapy. The demonstration of the efficacy of strontium-89 when compared with placebo will lead to further clinical trials to assess the potential of strontium-89 not only for prostate cancer but also for other malignancies that frequently metastasise to bone.

Clinical trials are now underway comparing the efficacy of strontium-89 with hemibody radiotherapy and evaluating the efficacy of strontium-89 as an adjuvant to local-field radiotherapy in patients who present with less advanced disease.

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Parental Employment at Time of Conception and Risk of Cancer in Offspring

Jørgen H. Olsen, Peter de Nully Brown, Gabi Schulgen and Ole Møller Jensen

Studies on the possible association between exposures of parents at the time of conception and cancer in their offspring have provided no clear answer. In this large, population-based, record-linkage study, 1747 childhood cancer cases were identified in the Danish Cancer Registry and matched with 8630 population controls. Specific information on the employment held by each parent at the time of conception and during early pregnancy was obtained through record linkages. The most recent job titles of the parents were also supplied. Significantly increased risks for renal cancer (mainly Wilms' tumour) and for osteogenic and soft tissue sarcomas were observed in children in association with mothers' employment in medical and dental care, based on 15 observations and odds ratios (OR) of 2.5–4.0. The risk for cancers at all sites was significantly elevated in children of female nurses (OR = 1.4; n = 75) and of male and female physicians, dentists, dental assistants, veterinarians and pharmacists combined (OR = 1.4; n = 53). Handling of drugs, exposure to anaesthetics and infections during pregnancy are suggested to be potential risk factors. Significantly increased risks were also observed for children of fathers employed in the manufacture of iron and metal structures (OR = 2.2; n = 16), in machine repair workshops (OR = 2.8; n = 6), as machinists (OR = 1.6; n = 47) and as smiths (OR = 1.5; n = 28). The suggestion in earlier studies that exposures to hydrocarbons and lead are risk factors for childhood cancer could not be supported by our analysis. Overall, few associations were observed; it was therefore concluded that parental occupation is not likely to be a major risk factor for childhood cancer.
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INTRODUCTION

THE INITIAL peak of cancer incidence during the first 5 years of life can plausibly be explained as the result of prenatal mutagenic exposures such as those of parents during the working day. Accordingly, many studies have been conducted to evaluate potential associations between the occupational activities of the parents and the risk for cancer among their offspring [1–25]. A number of occupational exposures, particularly of men, have been suggested as potential risk factors [1–16], and a few general tendencies appear: an increased risk for cancer among offspring of fathers occupied as mechanics, machinists or painters, and of fathers employed in subsections of the iron and metal industries [1–4, 6, 9, 12, 13]. Exposure of mothers to "chemicals" during work has also been cited as a risk factor for childhood cancer [4, 8]. Exposures of parents to hydrocarbons, lead, solvents, paints and exhaust gases from motor engines have been hypothesised as specific causes, but, other studies have not substantiated this association [3, 10, 17, 20, 21, 24].

Thus, the results reported to date on the association between childhood cancer and parental occupation are largely inconsistent. This may be due to the hypothesis-generating nature of most of the studies or to variation in the terminology of occupations applied in the different studies. Furthermore, in all of the studies, the numbers of specific types of childhood cancer are relatively small and often insufficient for detailed analyses.

We report the findings of a large, population-based record linkage, which was set up specifically to investigate the possible importance of parental employment at the time of conception for the risk that their offspring will develop cancer before the age of 15.

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