two cases. In the remaining patients who received analgesia no delay in definitive management occurred. Of equal importance was the observation that the surgical registrar's confidence in diagnosing and in deciding on management was not affected by previous administration of papaveretum.

The correct management of patients presenting with acute abdominal pain includes diagnosis, resuscitation, and early operative intervention when indicated. Regrettably, definitive management decisions by surgical registrars are sometimes delayed in less severely ill patients by other clinical commitments such as outpatient clinics and operating lists. Furthermore, many hospitals do not have operating time allocated separately for surgical emergencies during working hours so surgery on patients with acute illness may be delayed until the last elective operating list is finished. These delays, added to the time between seeing a general practitioner and being transferred to hospital, all add to the patient's distress. We believe that this study shows that early pain relief with papaveretum in patients with severe acute abdominal pain does not have any adverse effect on their diagnosis and management. As it is every doctor's duty to relieve suffering when he or she can, patients presenting with acute abdominal pain should not be excluded. The recent recommendations by the Committee on the Safety of Medicines suggest that morphine is more appropriate for women of childbearing age.[13]

Although not the focus of this study, our results suggest that general practitioners should be encouraged to give pain relief to patients with significant abdominal pain when appropriate. This should not affect subsequent management and will reduce their patients' suffering during transfer to hospital.

The editorial in the *BMJ* 13 years ago recommended early pain relief in the management of acute abdominal pain.[2] This study provides the scientific data to justify this recommendation.

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Effect of salcatonin given intranasally on bone mass and fracture rates in established osteoporosis: a dose-response study

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Abstract

***Objective*—To study the dose related response of salmon calcitonin (salcatonin) given intranasally on bone mass and bone turnover and the effect of salcatonin on rates of fracture in elderly women with moderate osteoporosis.**

***Design*—Double blind, placebo controlled, randomised group comparison.**

***Setting*—Outpatient clinic for research into osteoporosis.**

***Subjects*—208 healthy women aged 68-72 years who had a bone mineral content of the distal forearm on average 30% below the mean value for healthy premenopausal women.**

***Interventions*—The 208 women were allocated randomly in blocks of four to two years of treatment with either salcatonin 50 IU, 100 IU, or 200 IU given intranasally or placebo. All groups received a calcium supplement of 500 mg. 32 of the women left the study before its end and 164 women complied with the study criteria throughout.**

***Main outcome measures*—Bone mineral content of the distal forearm and lumbar spine and rates of vertebral and peripheral fractures after two years of treatment.**

***Results*—The average changes in bone mineral content of the spine showed positive outcomes of 1% (95% confidence interval −0·1% to 1·5%) in the group treated with calcium (placebo) and 3% (1·8% to 4·2%) in the group treated with salcatonin 200 IU. There was a significant dose related response to salcatonin, manifested by an increase of 1·0%/100 IU (0·2% to 1·7%, p=0·008). The rate of patients with new fractures was reduced significantly in the women treated with salcatonin to about one third of that in the non-salcatonin treated women (relative risk 0·23 (0·07 to 0·77)).**

***Conclusion*—The results suggest that, compared with calcium alone, salcatonin given intranasally reduces the rates of fracture by two thirds in elderly women with moderate osteoporosis. Furthermore, it increases spinal bone mass in a dose dependent manner.**

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Introduction

Osteoporosis is a major age related disease affecting millions of women throughout the world. It is characterised by a decreased amount of bone and increased susceptibility to fracture. No certain treatment is yet available for osteoporosis once it is established. Fluoride, which stimulates bone formation, has recently been questioned as to its effect on fracture rates.[1] Treatments that decrease bone resorption do not necessarily increase bone mass significantly and may not therefore prevent further fractures. Recent evidence has, however, suggested that oestrogen treatment in osteoporotic women significantly increases spinal bone mass[2] and reduces the rate of vertebral fracture.[3] Furthermore, it has been indicated that bisphosphonates reduce the incidence of vertebral fractures in osteoporotic women.[4,5]

The effect of calcitonin on the rate of fracture remains unknown, although injectable calcitonin has been approved for the treatment of established osteoporosis.[6] Calcitonin inhibits osteoclastic activity[7] and in the long term it affects the number of osteoclasts by inhibiting the production of osteoclast precursors.[8] The intranasal formulation was developed with the aim of reducing the incidence of systemic reactions and the

TABLE I—*Gross morphological and baseline values (means (SD)) of bone mass measurements and numbers of subjects (prevalence) with vertebral fractures according to two radiological methods in four treatment groups*

Treatment group	No of patients	Age (years)	Menopausal age (years)	Height (cm)	Weight (kg)	Bone mineral content of distal forearm (units)	Z score	Bone mineral content of lumbar spine (g)	No (%) of patients with vertebral fractures: Method of Kleerekoper *et al*[16]	No (%) of patients with vertebral fractures: Method of Melton *et al*[17]
Patients who completed study										
Salcatonin 50 IU	40	70 (1)	21 (5)	157 (5)	60 (11)	27·3 (3·1)	−3·2 (0·7)	34·7 (7·3)	4 (10·0)	5 (12·5)
Salcatonin 100 IU	43	70 (1)	24 (7)	159 (5)	62 (11)	27·4 (3·8)	−3·1 (0·9)	36·2 (6·5)	5 (11·6)	7 (16·3)
Salcatonin 200 IU	41	70 (1)	21 (4)	158 (7)	64 (9)	27·3 (3·8)	−3·2 (0·9)	36·3 (7·7)	6 (14·6)	6 (14·6)
Placebo	40	70 (1)	23 (5)	160 (6)	61 (9)	27·6 (3·1)	−3·1 (0·7)	35·8 (7·5)	2 (5·0)	4 (10·0)
Patients who entered study										
Salcatonin 50 IU	52	70 (1)	22 (5)	157 (5)	61 (12)	27·5 (4·3)	−3·1 (1·0)	34·6 (7·5)	7 (13·5)	8 (15·4)
Salcatonin 100 IU	52	70 (1)	23 (7)	159 (5)	62 (11)	27·1 (3·8)	−3·2 (0·9)	36·2 (7·1)	5 (9·8)	8 (15·4)
Salcatonin 200 IU	52	70 (1)	22 (5)	159 (7)	63 (9)	27·0 (3·6)	−3·2 (0·8)	35·8 (7·1)	7 (13·5)	7 (13·5)
Placebo	52	70 (1)	23 (5)	160 (5)	63 (10)	27·9 (3·2)	−3·0 (0·7)	35·6 (7·2)	2 (3·9)	4 (7·7)

discomfort of the injectable form, thereby improving compliance. Clinical studies have shown that the intranasal administration of calcitonin reduces subsequent bone loss in patients with established osteoporosis, but the relation to dose is unknown.[9-11]

The aim of this study was to examine the dose related effect of salmon calcitonin (salcatonin) (Sandoz AS) given intranasally on bone mass and bone turnover and the effect of salcatonin on the rates of fracture in a two year prospective, randomised, double blind, placebo controlled study.

Subjects and methods

The participants were recruited by questionnaires sent to all women aged 68-72 years in six municipalities near Glostrup Hospital. Of the 2009 questionnaires sent out, 1522 were returned,[12] and 788 women met the primary selection criteria—that is, they did not suffer from immobility; had never had coronary infarction, stroke, or malignancy; and were not taking sex hormones or other drugs affecting calcium metabolism. These women were invited to a medical screening, which included examination of calcium metabolism. Of the 512 who attended, 270 women had a bone mineral content of the distal forearm at least 2 SD below the mean value for healthy premenopausal women and none had diseases known to affect calcium metabolism.

These women were invited to participate in a two year, placebo controlled, randomised, double blind study of the dose-response effect of salcatonin given intranasally, and 208 (77%) agreed. Informed consent was obtained from each subject and the protocol was approved by the local ethics committee. Participants were allocated by random sampling numbers in blocks of four to daily intranasal treatment with either salcatonin 50 IU, 100 IU, or 200 IU or placebo. All participants received a daily supplement of calcium 500 mg. Visits were scheduled every three months throughout the two years.

COMPLIANCE

Of the 208 women who entered the study, 176 (85%) completed the two year period. Eighteen women left the study because of intercurrent illnesses, 11 women because of adverse events, and three women for personal reasons or because of loss of interest. As 19 of these women left the study at three months and no follow up examinations were performed after the drop out time calculations were performed for those who completed the study.

The drop outs were distributed over the four groups as follows: 11 women receiving salcatonin 50 IU, six women salcatonin 100 IU, seven women salcatonin 200 IU, and eight women placebo. To ensure compliance patients were required to return all dispensed bottles at each clinic visit and on completion of the study. The amount of medication dispensed was compared with the amount returned, of which the approximate quantity—that is full, partial, empty—was noted. This information was checked against the total number of days of treatment. At the end of the two years 164 women had taken the treatment as prescribed[13] and still fulfilled the selection criteria ("valid completers"). Thus seven women had omitted to take the required 75% or more of the dispensed medication, two had taken oestrogen for two to four weeks, one had received low dose glucocorticoid treatment, and two had exclusion conditions which were diagnosed at the final examination.

MEASUREMENT OF BONE MASS

The bone mineral content of the distal forearm was measured by single photon absorptiometry with an iodine-125 source (3·7 GBq) with photopeak at 27 keV.[14] Bone mineral content is determined as the mean of six scans 4 mm apart just proximal to the site where the distance between the ulna and the radius is 8 mm. In our department the long term in vivo precision of this method is 1%.

The bone mineral content of the lumbar spine was measured by dual energy *x* ray absorptiometry (Hologic, model QDR-1000).[15] This system uses a highly collimated dichromatic *x* ray source (70 kVp and 140 kVp). The bone mineral content is calculated in L2 to L4, including the intervertebral discs, systematically in all patients and expressed in grams after internal calibration. In our department the long term in vivo precision of this method is 1·5%.

TABLE II—*Baseline values (means (−1 SD to +1 SD)) for biochemical parameters in four treatment groups*

Treatment group	No of patients	Plasma bone Gla protein (ng/l)	Serum alkaline phosphatase (U/l)	Fasting urinary hydroxyproline corrected for creatinine (mmol/mol)	Serum calcium/protein (mmol/g)	Serum phosphate (mmol/l)
Patients who completed study						
Salcatonin 50 IU	40	11·9 (7·7-18·5)	192 (150-243)	15·6 (11·9-20·4)	2·37 (2·28-2·46)	1·1 (1·0-1·2)
Salcatonin 100 IU	43	10·9 (7·6-15·7)	178 (142-224)	13·6 (10·1-18·4)	2·34 (2·25-2·44)	1·1 (1·0-1·3)
Salcatonin 200 IU	41	9·9 (6·3-15·5)	177 (148-212)	13·4 (9·6-18·7)	2·36 (2·28-2·45)	1·1 (1·0-1·2)
Placebo	40	10·5 (6·6-16·9)	167 (135-205)	14·1 (10·2-19·6)	2·37 (2·29-2·46)	1·1 (1·0-1·3)
Patients who entered study						
Salcatonin 50 IU	52	11·4 (7·2-18·0)	188 (148-240)	15·6 (12·1-20·1)	2·37 (2·28-2·46)	1·1 (1·0-1·2)
Salcatonin 100 IU	52	10·8 (7·5-15·6)	175 (138-223)	13·7 (10·1-18·5)	2·34 (2·25-2·44)	1·1 (1·0-1·3)
Salcatonin 200 IU	52	10·4 (6·6-16·3)	182 (151-219)	13·8 (9·9-19·2)	2·36 (2·28-2·45)	1·1 (1·0-1·2)
Placebo	52	10·3 (6·6-16·0)	172 (139-214)	14·3 (10·5-19·3)	2·37 (2·28-2·45)	1·1 (1·0-1·3)

MEASUREMENT OF BONE TURNOVER

Blood samples were taken and urine collected in the morning after an overnight fast and abstinence from tobacco. Serum alkaline phosphatase, plasma bone Gla protein (indicators of bone formation), and fasting urinary hydroxyproline corrected for creatinine excretion (an indicator of bone resorption) were measured by standard procedures.

MEASUREMENT OF BIOAVAILABILITY

The acute dose-response bioavailability of the intranasally administered salcatonin was examined at the time of entry into the study. Blood samples were collected from each participant before and 15 minutes after administration of the randomised medication. The concentrations of circulating immunoreactive salcatonin were measured by radioimmunoassay by using polyclonal sheep antiserum. The accuracies of quality controls were −1·1%, 1·6%, and 6%; the detection limit was 0·010 mIU/ml; and the intra-assay and interassay variations were 8% and 13%.

ASSESSMENT OF VERTEBRAL AND PERIPHERAL FRACTURES

Every year the thoracic and lumbar spines were radiographed with the participant lying in a fixed lateral position under standardised conditions with a fixed film-focus distance. At the end of the study each participant's radiographs were displayed simultaneously in chronological order for blind assessment of vertebrae T4 to L5. Two methods were used to assess the radiographs for fractures, and for both methods the anterior, midvertebral, and posterior heights on each vertebra were measured to the nearest millimetre with a transparent ruler. Intraobserver variation was 2·5% (range 1·5-3·8%).

Method of Kleerekoper et al[16]—Wedge deformities were defined as a reduction of at least 25% in anterior height as compared with posterior height; compression deformities had to have a reduction of at least 25% in posterior height as compared with that of adjacent vertebrae.

Method of Melton et al[17]—Wedge and compression deformities were basically defined on the same criteria as in the method of Kleerekoper *et al* except that the reduction had to be at least 20%. Before these criteria were applied the height of each measurement was corrected by an adjustment factor that took into account the normal variation in vertebral shape and size throughout the spine between (*a*) the anterior and posterior heights and (*b*) the posterior heights and those of adjacent vertebrae. The adjustments were made on the data of 31 healthy early postmenopausal women who had no radiological evidence of vertebral fractures.

Peripheral fractures were checked with medical records and radiographs. Only non-traumatic fractures and fractures caused by minor trauma were considered osteoporotic.

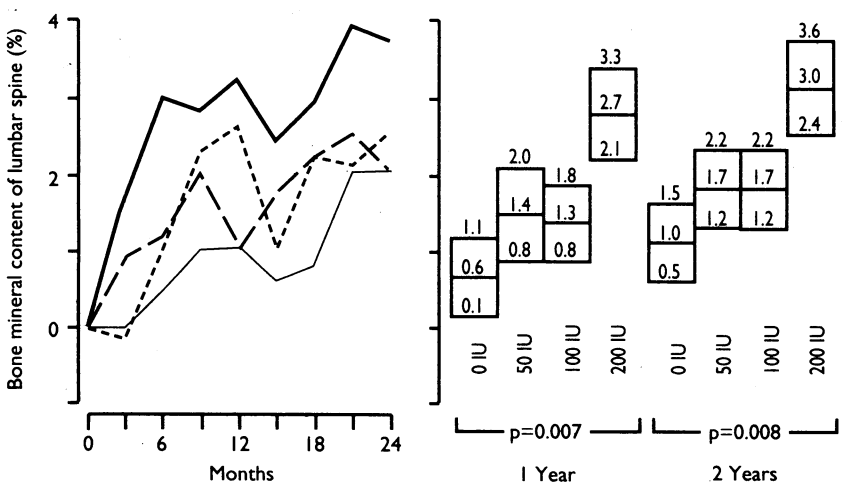

FIG 1—*Bone mineral content of lumbar spine during two year study with salcatonin (left) and average (SE) changes at one and two years (right). ——=Placebo. - - - -=50 IU salcatonin. — — —=100 IU salcatonin. ——=200 IU salcatonin. p Values are given for dose relation (linear regression analysis)*

Statistical analysis

Fifty two women were assigned randomly to each of the four treatment groups. This sample size would detect a difference of 2% between two groups with the type I error of 5% and the type II error of 10%, assuming a precision of 3% of the bone mineral content of the lumbar spine. The procedures of the Statistical Analysis System were applied. All the randomised participants who completed the study (n=176) were used in the analysis of the two year response to treatment, even though some did not administer the treatment as prescribed.[13] A "valid completers" analysis (n=164) was also done and, unless otherwise stated, it is on this that the results are based.

The comparability of the four treatment groups at baseline was assessed as appropriate by one way analysis of variance or Fisher's exact test. The biochemical parameters of bone turnover were logarithmically transformed to normalise variations. The serial measurements of bone mass and bone turnover during the two years were analysed according to the concept described by Matthews *et al*.[18] The average changes during treatment were calculated for each woman after one and two years and used as summary measures of the one and two year responses to treatment. The summary measures were compared across treatment groups by analysis of variance. The response in bone turnover was related to the pretreatment values, which, despite randomisation, differed between groups. To account for this the analyses of the bone turnover parameters were adjusted for baseline values by analysis of covariance. When analysis of variance revealed borderline significance (p values less than 0·20) the power was increased applying information on the dose. A linear increase or decrease with increasing calcitonin dose was used as an alternative to the hypothesis that no dose related response to calcitonin treatment exists (linear regression analysis). A higher or lower response in the pooled salcatonin groups than in the placebo group was used as an alternative to the hypothesis of no calcitonin effect when no dose relation was observed.

The bioavailability of salcatonin given intranasally was expressed in medians and analysed for dose relation by the Spearman test. Groups were compared on rates of new fracture patients/rates of patients with new fractures by Fisher's exact test. To make comparison with other studies possible the rates were expressed as the number per 1000 person years and the relative risks were calculated.

All tests were two tailed and $p<0·05$ was considered significant.

Results

Table I gives the gross morphological and baseline values of bone mineral content, Z scores, and numbers of patients with vertebral fractures. The data show that the three treatment groups were well matched with the placebo group and that this was the case both for the total number of randomised women and for the "valid completers." Table II shows the baseline values for indicators of bone turnover. Despite randomisation the concentration of serum alkaline phosphatase was significantly higher in the group receiving salcatonin 50 IU than in the other three groups (p=0·040). The other biochemical parameters showed the same pattern.

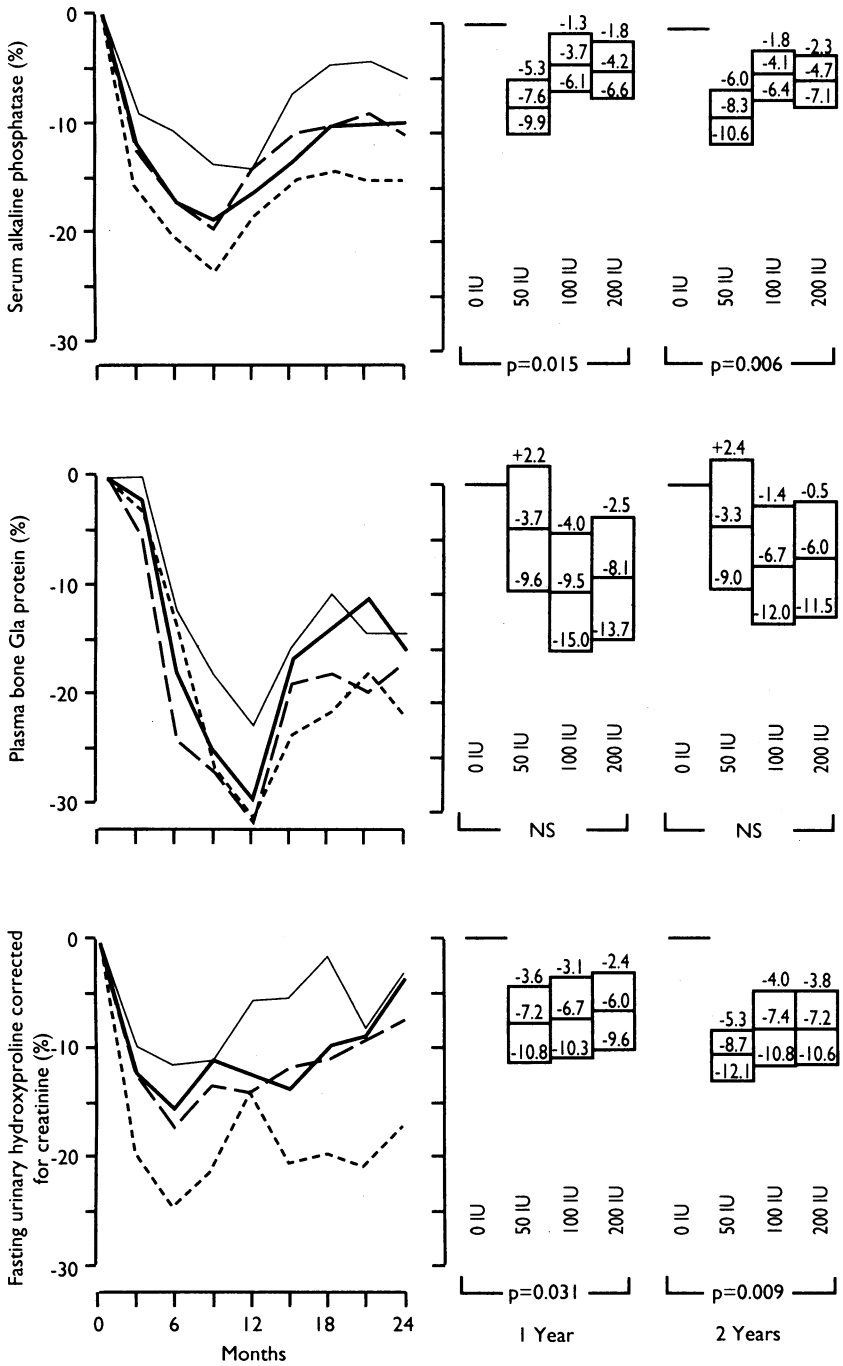

FIG 2—*Indicators of bone turnover during two year study with salcatonin (left) and average (SE) changes adjusted for initial values and placebo effect at one and two years (right). ——=Placebo. – – –=50 IU salcatonin. – – –=100 IU salcatonin. ——=200 IU salcatonin. p Values are given for placebo versus salcatonin treatment (t test)*

Figure 1 shows the serial measurements of the bone mineral content of the lumbar spine (mean percentages) over the two years according to group. The average changes were similar after one and two years (right) and showed positive outcomes of 1-3% in all groups (analysis of variance: p=0·048, 0·057)—after two years 1% (95% confidence interval 0% to 2·0%) in the group treated with calcium alone (placebo) and 3% (1·8% to 4·2%) in the group treated with salcatonin 200 IU. There was a significant dose related response to salcatonin, revealing an increase of 1·0%/100 IU both after one year (0·3% to 1·7%, p=0·007) and after two years of treatment (0·2% to 1·7%, p=0·008). Similar results were seen for all the women who completed the two year period (n=176).

The average changes in the bone mineral content of the distal forearm showed negative outcomes of about 0·5% after one year and of about 1% after two years in all groups (analysis of variance: NS)—after two years −1·2% (−2·1% to −0·3%) in the group given calcium alone (placebo) and −0·9% (−1·6% to −0·2%) in the group given salcatonin 200 IU (data not shown).

Figure 2 visualises the serial measurements of serum alkaline phosphatase, plasma bone Gla protein, and fasting urinary hydroxyproline corrected for creatinine (mean percentages) over the two years according to group. The average changes in the groups receiving salcatonin were similar after one and two years (analysis of variance: serum alkaline phosphatase, p=0·029, 0·011; fasting urinary hydroxyproline corrected for creatinine, p=0·190, 0·070). There was no dose related response to salcatonin, but a significant difference between the response to salcatonin and calcium alone (placebo) was observed after both one and two years (right) for serum alkaline phosphatase (p=0·015, 0·006) and fasting urinary hydroxyproline corrected for creatinine (p=0·031, 0·009). After two years the difference was −5·6% (−9·4% to −1·6%) for serum alkaline phosphatase and −7·8% (−13·2% to −2·0%) for fasting urinary hydroxyproline corrected for creatinine. Similar results were seen for all the women who completed the two year period (n=176). The same pattern was seen for plasma bone Gla protein but it did not reach statistical significance (difference −5·4% (− 14·2% to 4·3%) after two years).

The absolute bioavailability of the three doses of salcatonin increased twofold and fourfold over the dose range 50-200 IU (p<0·001), resulting in similar values for the dose corrected bioavailability (data not shown).

Table III gives the numbers of patients with new fractures, either vertebral or peripheral, during the two years. There were fewer new patients with vertebral fractures by both radiological methods and fewer new patients with peripheral fractures in all three groups receiving salcatonin than in the group receiving placebo. Because of this and the small number of new patients with fractures in all four groups the results from the three salcatonin groups were pooled.

Figure 3 illustrates the incidence per 1000 person years of new patients with vertebral fractures alone (assessed by the two radiological methods) and new patients with vertebral plus peripheral fractures during the two year study. The figure also visualises the rates of new fractures per 1000 person years. Both the incidence of new patients with fractures and the rates of new fractures were reduced significantly in the salcatonin treated group to about one third of that in the non-salcatonin treated group (relative risks 0·23 (0·07 to 0·77) to 0·37 (0·14 to 0·95)). A similar reduction was seen for all the women who completed the two year period (n=176). According to the method of Kleerekoper *et al* 12 of the valid completers (n=164) had sustained one wedge fracture and three women had two; according to the method of Melton *et al* nine women had one wedge fracture and two women two, and one woman had one compression fracture. The osteoporotic peripheral fractures were three in the forearm and one in the humerus.

There was virtually no difference between the rates of adverse events in the salcatonin groups (25-33%) and that in the placebo group (23%). General adverse events were headache, dizziness, nausea, and constipation. Local adverse events were primarily nasal secretion and sneezing, nasal dryness, and nasal crusts. Irritation of the nasal mucosa occurred in two women receiving salcatonin. There were no clinically significant changes in safety parameters such as blood pressure and blood chemistry.

Discussion

This study shows for the first time a reduction of two thirds in the incidence of new patients with fractures and the rates of new vertebral and peripheral fractures

TABLE III—*Numbers of new patients with vertebral and peripheral fractures during two year study of intranasally administered salcatonin*

Treatment group	New patients with vertebral fractures		New patients with peripheral fractures	New patients with fractures	
	Method of Kleerekoper *et al*[16]	Method of Melton *et al*[17]		Method of Kleerekoper *et al*[16]	Method of Melton *et al*[17]
Salcatonin 50 IU	1	2	1	2	3
Salcatonin 100 IU	1	0	1	2	1
Salcatonin 200 IU	3	2	0	3	2
Placebo	7	6	2	9	8

in salcatonin treated women compared with non-salcatonin treated women. A significant dose related increase in spinal bone mass was also found. The study was conducted with a large, homogeneous, and representative group of elderly osteoporotic women as defined by a bone mineral content of the distal forearm, which averaged 30% below that of healthy premenopausal women.

The present study, unlike other fracture studies,[1 3-5] selected the participants based on low bone mass and not on pre-existing fractures. This enabled us to investigate the incidence of new patients with fractures in addition to the rates of new fractures. Other fracture studies have included women with pre-existing fractures because they seem to sustain new fractures more easily.[19] Our selection based on low bone mass strengthens the evidence of a reduced rate of new fractures in women treated with salcatonin compared with non-salcatonin treated women.

It is well known that quantitative and qualitative radiological methods show discrepancies in the diagnosis of vertebral deformities.[20] We used a quantitative method and exact height measurements and applied a 25% unadjusted and a 20% adjusted limit for height reduction. These definitions ensure an appropriate degree of deformity. Although there is no general agreement as to what constitutes a vertebral fracture, it is recognised that considerable reductions must be present to define vertebral deformities as osteoporotic manifestations.[21] Otherwise an unreasonable number of vertebrae would be classified as fractured. Anatomically, for instance, the anterior heights relative to the posterior heights are less for the midthoracic vertebral bodies than for the lower thoracic and lumbar areas, which gives a false impression of wedge fracture. As the adjusted radiological method of Melton *et al*[17] accounts for such normal variations we chose a lower reduction limit for the adjusted method than for the unadjusted method.[16]

The rates of new vertebral fractures found in our study were comparable with those of a study of fracture and bisphosphonate treatment.[5] For the total number of participants the rates of new vertebral fractures over two years were 29·5/1000 patient years in the women given bisphosphonate versus 62·9 in the women not given bisphosphonate.

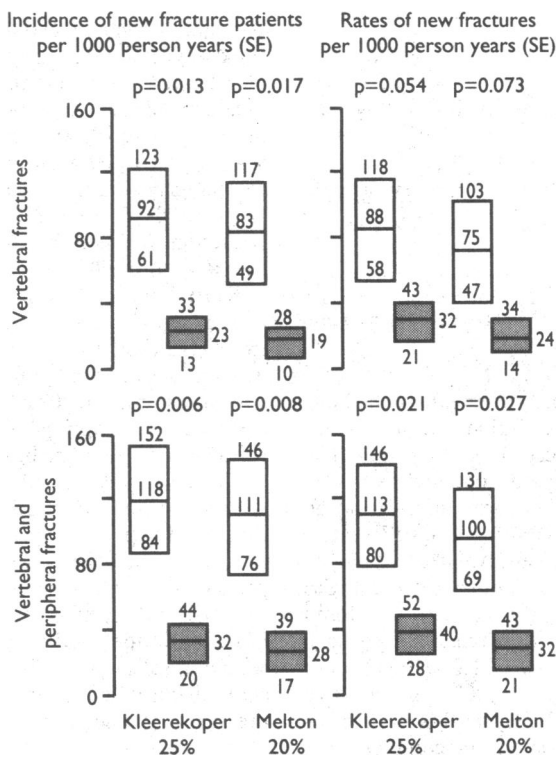

FIG 3—*Incidence of new patients per 1000 person years with vertebral fractures alone (diagnosed by two radiological methods) and vertebral plus peripheral fractures (left) and rates of new fractures per 1000 person years (right).* □ *=Placebo.* ▩ *=Salcatonin. Kleerekoper 25% and Melton 20% refer to specific radiological methods.*[16 17] *p Values by Fisher's exact test*

GREATER EFFECT IN THE SPINE

The effect of salcatonin on bone mass seemed to be more pronounced in the spine with a significant dose related increase of 1% per 100 IU administered over two years. Such differences between bone response in the spine and that in the forearm have been demonstrated in previous studies.[11 22-24] However, in a recent salcatonin study in 70 year old women we related the bone response to the previous bone loss and showed equal net outcomes in the forearm and spine.[23] Thus because at the age of 70 the bone loss in the forearm exceeds that in the spine[1 5 25] the net outcome of treatment with salcatonin would be a gain in spinal bone mass and a reduction of bone loss in the forearm. The present response in bone mass was supported by the modifications of bone turnover.

The difference of 2% between the active treatment and placebo groups in spinal bone mass was slightly lower than that of 3·5% observed by Watts *et al*.[5] Calcium was used as cotherapy in our study whereas phosphate was used in the study by Watts *et al*. In an earlier study by our group calcium had intermediate effects on bone mass and turnover compared with salcatonin treatment and no treatment.[9] It is well known that cotherapy and placebo effects may fill in part of the response window.[26] If both the cotherapy and placebo effects are taken into account higher differences than observed in the present study between the placebo and salcatonin groups could not be expected. For drugs with a larger response window the beneficial effects are, of course, easier to demonstrate. In a relatively small population of women with established osteoporosis a surprisingly high difference in the rates of vertebral fracture could be demonstrated after one year between the group treated with oestrogen and that not treated with oestrogen.[3]

In the present study the effect of salcatonin was most pronounced during the first year of treatment, when spinal bone mass increased and bone turnover decreased to a plateau. This is consistent with previous studies performed by our group, which indicated that treatment with salcatonin should be given discontinuously—for example, for one year followed by one year of withdrawal.[10 11]

We conclude that in elderly women with moderate osteoporosis administration of salcatonin intranasally reduces the rate of new fractures by two thirds compared with calcium treatment alone. Furthermore, it increases spinal bone mass in a dose dependent manner.

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HIV infection in a cohort of homosexual and bisexual men

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Epidemiological studies in the United States report rises in unprotected anal intercourse among gay and bisexual men,[1] after dramatic reductions in the mid-1980s there[2] and in the United Kingdom.[3] In 1991 rising rates of rectal gonorrhoea among homosexual men attending genitourinary medicine clinics[4] led to speculation about increasing HIV risk behaviour in the United Kingdom.

This speculation is complicated by the bias in samples of clinic attenders towards more sexually active men but may be clarified by data from samples of non-attenders.

Subjects, methods, and results

In 1987-8 we interviewed a cohort of 930 homosexual and bisexual men in 10 cities in England and Wales who had been recruited from sources other than genitourinary medicine clinics. Subsequently 77%, 65%, and 50% were re-interviewed annually. All men were interviewed about current and past sexual behaviour. Respondents in London and South Wales were asked, though not required, to provide a blood sample for testing for HIV-1 antibody; for each year 344, 290, 240, and 296, about two thirds of those eligible, did so. The results, with counselling, were available to the men at their specific request. They were linked with behavioural data only for analysis. Ethical committee approval was obtained for all localities at each stage of the study.

The median age of the original cohort was 29 (range 15 to 81) years. Full details are given elsewhere.[5] The proportion of regular clinic attenders was 31% in 1987-8 and did not vary significantly. The proportion tested before the study began was 41%, rising in 1991 to 54% of the men interviewed.

The proportion of samples positive for HIV-1 antibody was significantly higher in the clinic attenders than non-attenders (15·6% *v* 3·8%; $\chi^2=11·35$, $p=0·0018$).

Unprotected anal intercourse was more common in men in regular than in casual relationships (19% *v* 4%). The mean annual number of partners with whom anal intercourse occurred increased from 2·0 in 1987-8 to 2·7 in 1990-1, and the number of partners increased from 12·3 to 17·9 ($t=2·53$, $p=0·011$). Meanwhile, the proportion reporting oro-anal contact in the month before interview rose from 31% to 41% and reporting digital-anal contact from 42% to 57%.

Seventy three men in the cohort were antibody positive, some of whom subsequently died; 13 do not know their HIV status. Eleven (15% of all positive) men who were antibody negative in 1987-8 subsequently tested positive. The mean period between the positive result and the last negative result was 11 (range 2 to 24) months. In 10 men we could identify the year of seroconversion: our best estimates are 1987, one man; 1988, two; 1989, two; 1990, three; and 1991, two.

All 11 men reported unprotected anal intercourse and a range of other sexual acts before seroconversion. In five unprotected receptive anal intercourse was the probable mode of transmission. In two men unprotected insertive intercourse was the likely mode, but both had also practised receptive fellatio with orgasm, one with a partner known to be antibody positive and one had also engaged in insertive fisting. In the four other men both unprotected receptive and insertive anal intercourse had occurred.

In eight men, the source of infection was clearly identified as a regular partner four of whom were known to be antibody positive at the time. In only one man was the source clearly traced to a casual partner. Three of the seroconversions were not in regular clinic attenders, nor had the men attended in the year before interview. Four men had not previously been tested.