The Effect of Calcitriol on Patients with Postmenopausal Osteoporosis with Special Reference to Fracture Frequency (42922)

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Malabsorption of calcium is a common finding in patients with postmenopausal osteoporosis (1, 2). In a number of studies serum 1,25 dihydroxyvitamin D levels were found to be significantly lower in osteoporotic patients, which could account for the calcium absorptive defect (3–6). Based on these findings, we studied the effects of synthetic calcitriol (Rocaltrol) in women with osteoporosis. We showed that calcitriol, 0.25 μg twice daily, improved and normalized the absorption of calcium in all patients and improved calcium balance (7). Urine hydroxyproline, which is a measure of bone resorption, decreased significantly after 2 years of treatment with Rocaltrol. Because of these preliminary findings, further clinical studies were carried out at two centers using a variable dose of Rocaltrol. In these studies we focused on the effectiveness of Rocaltrol in preventing vertebral fractures in patients with spinal osteoporosis.

Methods

The results from two centers have been analyzed both as separate groups and as one combined group. One study was performed at the Mayo Clinic (Protocol 861) and the other at Creighton University (Protocol 860). In both centers the studies performed were double blind and randomized, and compared the effect of placebo against Rocaltrol for a period of 1 year. At the end of 1 year all patients on placebo were crossed over to treatment with Rocaltrol and followed for 2 more years. Patients initially treated with Rocaltrol were followed for an additional 2 years, thus yielding treatment data extending to 3 years in a number of patients. In the study design, patients were given Rocaltrol at a starting dose of 0.25 μg twice daily, if hypercalcemia and hypercalciuria did not occur the dose then was increased to 0.75 μg or 1.0 μg daily at the discretion of the investigator. Hypercalcemia was defined if a serum calcium >11.0 mg/dl and hypercalciuria occurred if the 24-hr urine calcium >350 mg. All patients followed a free calcium intake during the study. In order to satisfy the entry criteria for study, patients had to have definite evidence of one or more vertebral fractures with no obvious history of trauma. Also, patients had to have normal liver and renal function and no obvious disease or drug history known to be associated with a disturbance of calcium metabolism. All patients underwent an iliac crest bone biopsy so as to exclude histologic evidence of osteomalacia.

Fracture Definition

For the purpose of fracture analysis, the same criteria for defining vertebral fractures were used in both centers. All patients underwent baseline lateral x-rays of the thoracic and lumbar spine. A vertebral fracture was diagnosed if the anterior height of the vertebra was 25% less than the posterior height. Lateral views of the spine were repeated after 1, 2, and 3 years of treatment. Further fractures during the course of the study were noted if the anterior height of the vertebrae decreased by 15% from the baseline measurement. The number of new fractures were expressed as a fracture rate per thousand patient years. It is important to state that many of the recurrent fractures were subclinical without pain, so that this definition of fracture is a measure of the change in shape of a vertebra. In each center x-rays were read blind by two observers without knowledge of the treatment group.

Final Distribution of Patients after Randomization

After double-blind randomization of 31 patients at Creighton University, 18 patients completed 1 year on placebo, of whom 15 were suitable for analysis. Thirteen patients were treated with Rocaltrol, of whom 11 were suitable for analysis. Of the 5 patients excluded from analysis, one patient died, one patient dropped out of the study before the end of 1 year, and three patients did not satisfy the initial criteria for definition of an osteoporotic fracture. In the Mayo Clinic study, 40 patients were randomized to treatment or placebo. In the first year, 18 patients completed 1 year of obser-

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vation on Rocaltrol and 2 dropped out. Eighteen patients completed 1 year on placebo and 2 dropped out. Of the four patients excluded from analysis, all were due to drop outs before the end of the first year of study. In Year 2 of the study all patients in both centers were crossed over to active treatment. In the Creighton study, all 15 patients on placebo crossed over to Rocaltrol and completed 1 year of treatment, 13 patients completed 2 years on Rocaltrol, and none completed 3 years. In the Creighton group initially randomized to Rocaltrol, 11 patients completed the first year of treatment, 9 completed the second year, and 8 completed the third year of treatment. In the Mayo Clinic study, 14 of the 18 patients on placebo crossed over to Rocaltrol treatment and completed 1 year of treatment, 12 continued for 2 years of treatment, and none proceeded to 3 years. Of the 18 patients treated initially with Rocaltrol, 16 completed 2 years of treatment and 15 patients completed 3 years of treatment.

Statistics

Data were collected on the number of new fractures occurring between successive x-rays and on the length of time interval between x-rays, which was nominally 1 year, although it varied from 11 to 14 months. Fracture rates were then calculated for a given interval from the total number of fractures occurring in the interval divided by the sum of the time intervals (×1000). For analysis of the significance of change in fracture rates between treatment and placebo groups, the Poisson model was used: that is the probability of k fractures occurring in an interval of length t years with a fracture rate of λ (per patient years) follows the Poisson distribution:

$$P_k = \frac{(\lambda t)^{ke-\lambda t}}{k!}$$

This assumption is tested by a goodness of fit statistic. In order to examine the potential effect of Rocaltrol therapy, we treated each interval between x-rays as independent sampling units and looked at the distribution of the number of fractures in these intervals as a function of whether or not Rocaltrol therapy was given during the interval. Fracture rates were compared using the normal approximation to the Poisson distribution. In a further analysis we compared the number of fractures in the placebo after 1 year on placebo with that obtained after they crossed over and completed 1 year of Rocaltrol therapy. We applied McNemar's chi-square test for related samples to these frequencies. Finally, a Poisson regression model (8) was used to examine the effects of treatment, the previous number of fractures, and age on the fracture rate.

Results

Reliability of Vertebral Measurements. At the Mayo Clinic several patients underwent a second x-ray within 2 months of the original one. Repeat measurements were made on 80 vertebrae, and the repeat measurements on vertebral height showed the coefficient of variation for the method to be 3.2% (9). At Creighton University, using the same measurement technique for vertebral height on 70 vertebrae, we found the coefficient variation for repeat measurements to be 3.7% (10). Thus, the precision of measurement of vertebral height for both centers is similar with a coefficient of variation between 3 and 4%.

Presentation of Fracture Incidence. The mean age of the various subgroups, the initial number of fractures in the subgroups, the number of the patients who completed 1, 2, and 3 years of treatment, the number of fractures that occurred in that group, the number of patient years, and the calculated fracture rate expressed per thousand patient years are summarized in Table I. There was a systematic difference in the mean number of fractures at baseline in the two centers, 4.3 at Creighton vs 6.9 at Mayo; however, this difference falls just short of statistical significance ($P <$

Table I. Summary of Protocols 860 and 861

Group	Protocol	n	Baseline		Year 1[b]			Year 2[c]			Year 3[d]		
			Age	No. Fx[a]	Pt. years	No. Fx	Fx rate	Pt. years	No. Fx	Fx rate	Pt. years	No. Fx	Fx rate
Placebo group	860 (CU)[e]	15	65.1	4.33	17.4	15	862	16.8	7	417	16.6	2	121
	861 (MC)	18	62.7	7.11	21.5	17	791	13.5	3	222	12.4	3	242
	Combined	33	63.8	5.85	38.9	32	823	30.3	10	330	28.9	5	173
Treatment group	860 (CU)	11	63.8	4.27	12.4	2	161	9.5	3	315	12.2	2	164
	861 (MC)	18	61.7	6.78	20.9	13	623	15.5	6	387	14.7	2	136
	Combined	29	62.5	5.83	33.3	15	450	25.0	9	360	26.9	4	149

[a] Pt. years, patient years; no. Fx, number of fractures; Fx rate, fractures per 1000 patient years.
[b] Comparison of placebo vs treatment (Rocaltrol) in Year 1.
[c] Includes first year of Rocaltrol treatment for placebo group.
[d] Includes second year of Rocaltrol treatment for placebo group.
[e] CU, Creighton University; MC, Mayo Clinic.

0.08). Examination of the fracture rates in Table I shows that fracture rates appear to fall steadily as a function of years of therapy. The one exception is the relatively high fracture rate seen in the first year in the group randomized initially to Rocaltrol in the Mayo Clinic group.

If one assumes that the number of fractures occurring during an interval depends only upon the amount of therapy received, the data can be displayed according to these criteria as shown in Table II and Figure 1. Thus, the category (1 year of treatment) includes the first-year data from patients initially randomized to the Rocaltrol group as well as second-year data from patients in the placebo group who crossed over to complete their first year on Rocaltrol. The same analysis is performed for the second and third years. Again, the fracture rates appear to fall steadily as a function of years of treatment. The main difference from the data in Table I is that group sizes are now larger because the treatment group contains those patients who were crossed over from placebo to treatment.

Table II. Fracture Incidence Data by Years on Treatment

		Placebo	Years			
			1	2	3	1+2+3
Protocol 860 (CU)[a]	No. Fx[b]	15	9	5	2	16
	Pt. years	17.4	29.2	26.1	12.2	67.5
	Fx rate	862	308	192	164	237
Protocol 861 (MC)	No. Fx	17	16	9	2	27
	Pt. years	21.5	34.4	27.9	14.7	77
	Fx rate	791	465	323	136	351
Protocols combined	No. Fx	32	25	14	4	43
	Pt. years	38.9	63.6	54.0	26.9	144.5
	Fx rate	823	393	259	149	297

[a] CU, Creighton University; MC, Mayo Clinic.
[b] Pt. years, patient years; no. Fx, number of fractures; Fx rate, fractures per 1000 patient years.

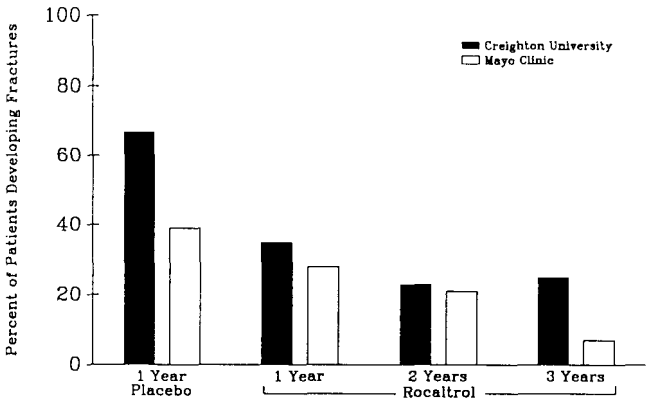

Figure 1. Effect of treatment with Rocaltrol or placebo on the vertebral fracture rate per 1000 patient years in postmenopausal osteoporotic patients (placebo was only given during the first year).

Statistical Analysis. The first number of analyses performed on this data tested the assumption that the distribution of the number of fractures followed a Poisson distribution. To do this the probability of 0, 1, 2, and 3 or more fractures in each interval was calculated, based upon the fracture rate and the length of the interval, and then summed across all intervals to arrive at the number of expected intervals with 0, 1, 2, etc., fractures. The observed number of intervals are then compared against these expected numbers using the usual chi-squared goodness of fit test. The results of this analysis are shown in Table III. The Poisson model appears to provide an adequate fit to the data for both placebo and treatment intervals.

Next we compared the fracture rate in the group given placebo for 1 year with either the group given Rocaltrol for 1 year or for the cumulative years 1, 2, and 3. None of the crossover data from the placebo group was included in this analysis. The results of the analysis are shown in Table IV. One-sided tests of significance are used since there is no a priori reason to hypothesize that Rocaltrol therapy increases the fracture rate. From Table IV the highly significant differ-

Table III. Goodness of Fit of Poisson Model to Fracture

No. of fractures	Placebo = 0.823		Treatment = 0.309	
	No. of intervals		No. of intervals	
	Observed	Expected	Observed	Expected
0	16	12.6	99	94.2
1	8	12.1	26	31.6
2	5	5.9	4	6.2[a]
3 or more	4	2.5	3	6.2[a]
	$\chi^2_2 = 3.34$ Nonsignificant		$\chi^2_2 = 1.34$ Nonsignificant	

Note. Chi-squares have degrees of freedom $n - 2$ since fracture rate is estimated from data.
[a] Cells pooled because expected frequency less than 1.

Table IV. Comparison of Placebo Group and Treatment Group Fracture Rates

Protocol	Placebo group			Treatment group			
	Year 1	Year 1		Years 1 & 2		Years 1–3	
	Fx Rate[a]	Fx Rate	*P*	Fx Rate	*P*	Fx Rate	*P*
860 (CU)[b]	862	161	0.003	228	0.005	205	0.003
861 (MC)	791	623	NS	522	NS	411	0.038
Combined	823	450	0.023	412	0.008	329	0.001

Note. Significance levels refer to test of equality of fracture rate vs alternative of treatment rate less than placebo rate. Test used is normal approximation to Poisson.
[a] Fx Rate, fractures per 1000 patient years.
[b] CU, Creighton University; MC, Mayo Clinic.

ences between the fracture rates of the placebo group and treatment group are apparent for the Creighton study group. In the Mayo group, however, only the difference between the placebo and the cumulative 3-year treatment fracture rate is significant. The reason for the discrepancy between the two centers is unknown. Because there is no corresponding discrepancy in the placebo group, this probably reflects the chance occurrence of an abnormally large number of fractures in the Mayo patients during their first year of therapy. (It is worth noting that 2 of the 18 patients contributed 7 of the 13 fractures in the first year.) The combined data shows significantly reduced fracture rates in the treatment group for the 1 year ($P = 0.023$), 2-years ($P = 0.008$), and all 3 years ($P = 0.001$).

In the previous analysis, we used the fracture rate per thousand patient years as the criterion for assessing the efficacy of a treatment regimen. However, because some patients have more than one fracture in a year, it is possible that a small number of patients markedly influence the fracture rate disporportionately. For these reasons we have performed a further analysis in which we looked only at the number of patients who had a fracture, whether one or more. We compared the placebo groups after 1 year on placebo with that obtained after they crossed over and completed 1 year on calcitriol. To do this, each of the 29 placebo patients who were followed for at least 2 years were categorized as to whether or not they had any fracture before and after treatment, the results are shown in Table V. Of the 29 patients, 13 had no fractures during their placebo or calcitriol years, 7 had at least one fracture during both periods, 8 had at least one fracture while on placebo, and none during their first year on calcitriol, while only one patient had no fractures on placebo and subsequently fractured during the first year on Rocaltrol. If we apply McNemar's chi-square test for related samples to these frequencies, it results in a χ^2 (corrected for continuity) of 4.00, $P < 0.05$, indicating that there is a significant association between the use of calcitriol therapy and the suppression of fractures. The percentage of patients who developed a fracture during Years 1, 2, and 3 is shown in Figure 2.

Poisson Regression Analysis. In this set of analyses, the data from all x-ray intervals were used and the data from both protocols combined. The basic approach taken here was to model the fracture rate in

Table V. Comparison of Placebo Group Years 1 and 2 (McNemar's Chi-Square Test)

		Year 2 (treatment)	
		No. fractures	One or more fractures
Year 1 (placebo)	No. fractures	13	1
	One or more fractures	8	7

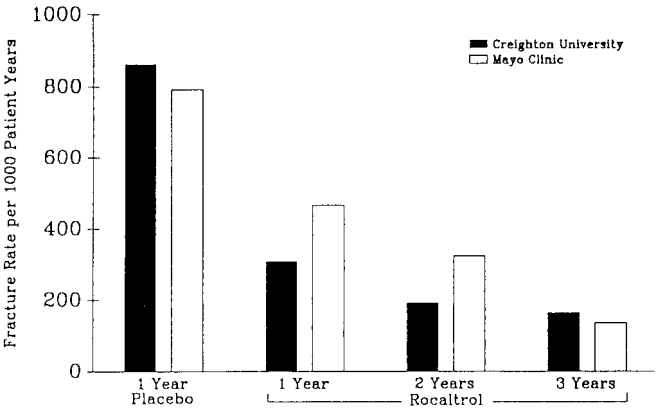

Figure 2. Effect of treatment with Rocaltrol or placebo on the percentage of osteoporotic patients who developed a vertebral fracture (placebo was only given during the first year).

each interval as a function of: (i) the number of years of therapy received = 0, 1, 2, or 3; (ii) the number of previous fractures experienced by the patient (including those from previous years of treatment); and (iii) age of the patient at the start of the interval.

The fracture rate for an interval is modeled as $\lambda = a_0 + [a_1 \times (\text{years of therapy})] + [a_2 \times (\text{number of previous fractures})] + [a_3 \times (\text{age})]$. This model assumes that the number of fractures occurring in an interval for a patient is dependent on the number occurring in a previous interval only through the corresponding change in the number of previous fractures. Again, assuming a Poisson model the likelihood or probability of observing this set of data is proportional to:

$$L = \prod_{i=1}^{N} (\lambda_i t_i)^{f_i} e^{-\lambda_i t_i}$$

where N is the number of intervals analyzed, λi is a function of above observed data in the i^{th} interval and unknown parameters given above, t_i is the length of the i^{th} interval in years, and f_i is the observed number of new fractures in the i^{th} interval.

We want to find the values of the parameters a_0, a_1, a_2, and a_3 which maximize L, or equivalently minimize $-\ln(L)$. Using numerical optimization techniques, these values were found to be:

$$\hat{a}_0 = 0.363 \quad \hat{a}_1 = 0.15681$$

$$\hat{a}_2 = 0.015 \quad \hat{a}_3 = 0.003$$

and $\ln(L) = 123.15$.

Specific hypothesis may be tested by comparing the log likelihood under this full model with the log likelihood under the hypothesized model. For example, if we want to test the hypothesis that age has no effect we estimate a_1, a_2, and a_3 under the constraint that $a_3 = 0$. Under this hypothesis, $\ln(L)$ is 123.29.

An approximate χ^2 test that $a_3 = 0$ is given by the generalized likelihood ratio criterion as $\chi^2_1 = 2(123.29 - 123.15) = 0.28$ which is clearly nonsignificant. In a

similar manner we can test the joint hypothesis that $a_1 = a_2 = 0$ and $a_1 = a_2 = a_3 = 0$. The results of these analyses are shown in Table VI.

Although there may be a slight effect of a previous number of fractures, the most parsimonious of these models is one which includes not only the constant term but the effect of years of therapy. This model assumes a linear relationship of fracture rate with years on therapy. The next analysis used the maximum likelihood approach to test this assumption with the results shown in Table VIb. From Table VI, the only significant effect upon fracture rate is the presence or absence of calcitriol therapy. The data do not discriminate between a linear fall of fracture rate as a function of years of therapy and a single fracture rate appropriate for all treated patients. The effect of age on fracture rate seems to be minimal and the effect of previous number of fractures, while not statistically significant in this study, could possibly be a factor in the formation of new fractures.

Discussion

One of the difficulties of performing clinical trials with relatively small numbers of osteoporotic patients is that the random effects of fracture may distort the anaysis, either favorably or unfavorably. Other confounding variables may also influence the result. A bone remodeling cycle is typically 7 or 8 months in normal individuals and is often greater than a year in osteoporotic patients. Becauise of the long remodeling cycle, one might not expect to see an effect of treatment during the first year but rather in subsequent years. For this reason clinical trials in osteoporotics should probably extend for at least 2 years. The original study design, however, compared placebo against treatment for a period of only 1 year, before many of these points were fully appreciated. Although patients were followed for 3 years of treatment on Rocaltrol, the patients on placebo were followed for only 1 year. Despite the shortcomings of this design, fracture rates of 862 and 791 fractures per thousand patient years during the first year on placebo are similar to a value of 850 fractures/1000 patient years seen in a retrospective study of untreated patients (9).

The effects of treatment, age and previous fractures were tested in our study by the technique of Poisson regression analysis. These analyses showed that age had no effect on the fracture rate model, that the previous numbers of fractures had a slight though not significant effect, and that the best model was one that included only the constant term of the effect of years on therapy (Table VIa). This model assumed a linear relationship of fracture rate with years on therapy. However, the model incorporating a placebo fracture rate and treatment fracture rate (irrespective of length of time on treatment) fit equally well (Table VIb). It seems very likely that Rocaltrol was effective in reducing the number of vertebral fractures that otherwise would have occurred over a period of 3 years. Although it would be reasonable to assume that fracture rate would be a function of age and number of previous fractures, we were unable to show significance of either of these variables when incorporated into the statistical model. However, the effect of the previous number of fractures was just short of significance and although it seems reasonable to expect that patients with more severe osteoporosis would have more fractures it is not more than a suggestion in this study.

There are few long-term fracture studies available for comparison and certainly none with placebo-treated controls. Retrospective studies have shown a decrease in fracture rates with time using different treatment regimens (9). In a group treated with calcium supplements for 2.7 years, the fracture rate was 525/1000 patient years (419 excluding the first year), in a group followed for 4.5 years on estrogen and calcium the fracture rate was 200/1000 patient years (181 excluding the first year), a group treated with sodium fluoride and

Table VI. Analyses Results

a. Comparison of fracture rate models:
$\lambda = a_0 + a_1$ (years of therapy) $+ a_2$ (number of previous fractures) $+ a_3$ (age)
Parameter Estimates

Model	$\hat{a}_0$	$\hat{a}_1$	$\hat{a}_2$	$\hat{a}_3$	$-\ln(L)$	χ^2	*df*	*P*
Full model	0.363	−0.156	0.015	0.003	123.15	—	—	—
$a_3 = 0$ (no age effect)	0.516	−0.151	0.019	—	123.29	0.28	1	NS
$a_2 = a_3 = 0$ (no age or previous Fx effect)	0.657	−0.169	—	—	124.69	3.08	2	NS
$a_1 = a_2 = a_3 = 0$ (constant Fx rate)	0.421	—	—	—	132.90	19.5	3	<0.005

b. Test of linearity of fracture rates with time of treatment
Parameter Estimates

Model	$\hat{\lambda}_0$	$\hat{\lambda}_1$	$\hat{\lambda}_2$	$\hat{\lambda}_3$	$-\ln(L)$	χ^2	*df*	*P*
$\lambda = \lambda_i$ if *i* years of therapy	0.823	0.425	0.237	0.215	122.7	—	—	—
$\lambda = 0.657 - 0.169$ (years on therapy)	0.657	0.488	0.319	0.150	124.7	4.02	2	NS
$\lambda = \lambda_0$ if placebo, λ_1 if treatment	0.823	0.311	0.311	0.311	124.8	4.22	2	NS
Constant fracture rate	0.421	0.421	0.421	0.421	132.9	20.4	3	<0.005

calcium had a fracture rate of 220/1000 patient years (304 if the first year was excluded), and a group followed on sodium fluoride and estrogen for an average of 4 years had a fracture rate of 53/1000 patient years. Although these are retrospective analyses without control groups, the studies extend for varying periods of time and allow some comparison with the present study.

We have shown previously that malabsorption of calcium and low serum calcitriol contribute to negative calcium balance in osteoporotic patients (3). Also, synthetic calcitriol corrects the malabsorption of calcium and improves calcium balance (7). The results of these preliminary studies show that synthetic calcitriol also reduces the vertebral fracture rate. The data also support the concept that malabsorption of calcium and negative calcium balance contribute to bone loss and subsequent fractures. Further long-term studies of Rocaltrol which examine changes in bone density and fracture incidence, as well as potential side effects such as hypercalcemia and hypercalciuria, should provide a comparison of the risks and benefit of these compounds in the treatment of osteoporosis.

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