Role of Bone and Kidney in Tumor-Induced Hypercalcemia and Its Treatment with Bisphosphonate and Sodium Chloride

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The efficacy of intravenous aminohydroxypropylidene bisphosphonate as treatment for the hypercalcemia of malignancy was examined in a phase II multicenter study in 132 patients with a large variety of primary tumors. This provided an opportunity for an analysis of the separate influences of bone resorption and renal calcium handling on the genesis and maintenance of hypercalcemia. The results demonstrated that increased bone resorption is the major contributory factor and that inhibition with bisphosphonate normalizes the serum calcium concentration within five days in more than 90 percent of patients. Hypercalcemia is sustained by an inability of the kidney to deal efficiently with a chronically increased calcium load. This is influenced by the requirements of volume regulation in the presence of a sodium diuretic effect of hypercalcemia and is very sensitive to induced variations of sodium load. In addition, in a minority of patients, direct renal actions of tumor-derived humoral factors adversely reduce the ability to excrete calcium. For optimal treatment of tumor-induced hypercalcemia, bisphosphonate treatment should be combined with intravenous administration of saline solution.

Bisphosphonates inhibit bone resorption [1]. Treatment of tumor-induced hypercalcemia with the aminobisphosphonate 3-amino-1-hydroxypropylidene-1,1-bisphosphonate (APD) or the bisphosphonate dichloromethylidene bisphosphonate (Cl2MDP) rapidly and predictably restores the serum calcium concentration to normal [2–11]. Increased resorption of bone, by direct action of bone metastases on the skeleton or mediated through humoral factors elaborated by the tumor, is important in the pathogenesis of tumor-induced hypercalcemia [12]. There is also evidence of a renal contribution to the maintenance of hypercalcemia in many tumor patients. Their excretion of calcium is often diminished by a reduction in the glomerular filtration rate [13,14]; however, even when this is taken into account, they excrete a smaller fraction of the filtered calcium load than healthy persons after hypercalcemia of the same degree has been induced by short-term intravenous calcium infusion [3,4,15,16]. It has been suggested that this increase in renal tubular resorption of calcium is mediated by a primary action on the kidney of humoral factors elaborated by the tumors [16–18]. On the other hand, this increase in calcium resorption may reflect an adaptive increase of calcium-associated sodium resorption in the renal tubules, required for sodium homeostasis, since calcium infusion causes renal sodium loss [19,20] and sodium infusion causes calcium loss [3,4,10,17,21].

We have examined the efficacy of small intravenous doses of APD in a prospective multicenter study, encompassing a large number of hyper-

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calcemic patients with a representative variety of tumors [22]. The rapid normalization of serum and urinary calcium values confirmed the importance of increased bone resorption in the genesis of hypercalcemia. In addition to that, the study provided the opportunity for a retrospective analysis of the separate influences of calcium load and renal sodium handling on renal calcium transport. The relationship among these variables was examined in patients with various types of tumors and was subsequently compared with that in patients with primary hyperparathyroidism, patients with familial benign hypercalcemia, and healthy persons.

PATIENTS AND METHODS

Patients. This prospective study covered a period of two years and encompassed 132 consecutive patients from seven hospitals. Prior approval of the institutions' ethical committees and informed consent of patients was always obtained. Eligibility criteria included an uncorrected serum calcium concentration of more than 2.74 mmol/liter* and a histologically proved malignancy. Patients were excluded if they had received other drugs specifically directed against hypercalcemia or if treatment of the malignancy had been modified within the two weeks before the study or during the study. An exception to the latter occurred in 10 patients with breast cancer, who demonstrated hypercalcemia after the institution of hormonal therapy but in whom this therapy was continued throughout. Of the 132 patients studied, 74 were female and 58 male. Their ages ranged from 31 to 93 years, with a median of 61 years; two of the patients were children, eight and 14 years old. The coexistence of primary hyperparathyroidism was excluded on clinical grounds, and the parathyroid hormone level was normal or low in the 64 patients in whom it was measured. None had previously received bisphosphonates. Bone involvement was assessed by radiography and, if radiographic results were negative, by scintigraphy. The primary sites of malignancy, the presence or absence of bone involvement, and the major pertinent biochemical abnormalities are listed in **Table I.** The data for healthy persons and patients with familial benign hypercalcemia were reported previously [23]. The primary hyperparathyroidism in 12 patients (seven women and five men) was surgically proved. The age of these patients ranged from 50 to 66 years. The relevant data are also given in Table I.

Treatment Schedule. APD (15 mg dissolved in 500 ml of 0.9 percent sodium chloride, weight/weight) was administered intravenously over two hours. The infusions were repeated daily until one day after normalization of the uncorrected serum calcium concentration, but not for more than 10 days. Additional intravenous administration of saline solution (0.9 percent sodium chloride, weight/weight) was allowed; the quantity was left to the discretion of the treating physician, but was noted on the protocol. The analysis of the effect of saline administration on urinary calcium excretion pertains to 77 patients for whom complete sequential data on both urine calcium and sodium values were available. These patients have been divided into three groups: one consists of patients who received at least 1 liter of saline solution per day for more than 48 hours before and during APD therapy (n = 25, solid squares in Figure 3), the second group received the bisphosphonate without additional saline infusion either before or during the study (n = 18, solid circles), and the third group received no saline solution before APD therapy but began to receive infusion of more than 1 liter daily, when bisphosphonate administration was begun (n = 34, open squares). The amount of intravenous saline solution (0.9 percent sodium chloride) administered on the first day of APD therapy for these groups averaged 2.0 ± 0.2 (SEM), 0.5, and 2.8 ± 0.2 liters, respectively; the respective averages for initial serum creatinine values were 150 ± 31, 102 ± 8, and 147 ± 15 μmol/liter. The methods used for oral calcium loading in the healthy persons and in patients with familial benign hypercalcemia have been published [23].

Measurements. In the patients with tumors, fasting venous blood and concomitant urine samples were obtained daily; calcium, sodium, phosphate, and creatinine concentrations were assessed in the serum and urine, and albumin concentrations were measured in the serum. When pertinent data are incomplete with respect to urine samples, this is indicated in the results. Urinary excretion of solutes is expressed as the molar ratio to creatinine or as the ratio to the glomerular filtration rate. These are obtained through division of their concentration in the urine by the concomitant creatinine concentration (molar ratio) and by multiplication of this ratio with the serum creatinine (excreted calcium or excreted sodium). Post-treatment values were obtained one day after the last infusion of APD. Daily determinations pertinent to safety included peripheral blood cell counts and body temperature. Serum alkaline phosphatase activity, 5′-nucleotidase or gamma-glutamyl transpeptidase level, lactic dehydrogenase level, and erythrocyte sedimentation rate were measured before the start and one day after the end of treatment with APD.

Analytical Methods. All biochemical measurements were made with standard autoanalyzer techniques. The normal range for serum calcium is 2.25 to 2.56 mmol/liter, but allowance should be made for up to 4 percent variation in the results due to differences between laboratories. With the exception of Figure 1, in which total serum calcium values are shown, corrections for albumin have been applied, by subtracting or adding a calcium value of 0.02 mmol/liter per 1.0 g of albumin in excess of or below 40 g/liter. Renal tubular phosphate reabsorption capacity was assessed in relation to the glomerular filtration rate with a nomogram [24]. Urine hydroxyproline (normal values up to 30 mol/mol creatinine × 10^3) was measured in only 28 patients from one of the participating hospitals according to the method of Prockop and Udenfriend [25]. The Student t test was used for comparison between paired and unpaired samples and analysis of variance for correlations [26]. Results were regarded as having no significance if at a p value of more than 0.05.

* Conversion of SI to traditional units: calcium, 1 mmol/liter ≅ 4 mg/dl; phosphate, 1 mmol/liter ≅ 3.1 mg/dl; creatinine, 100 μmol/liter ≅ 1.1 mg/dl; urinary calcium, 1 mol/mol creatinine ≅ 350 mg/g; urinary phosphate, 1 mol/mol creatinine ≅ 275 mg/g; urinary sodium, 1 mol/mol creatinine ≅ 8.8 mmol/g.

TABLE I Characteristics and Pre- and Post-Treatment Biochemical Values (mean, SEM) in 132 Patients with Tumor-Induced Hypercalcemia and Three Groups of Control Subjects

	Serum				Urine					
	Number*	Calcium (mmol/liter)	Albumin (g/liter)	Creatinine (μmol/liter)	Number†	TmP/GFR‡ (mmol/liter)	Calcium/ Creatinine (mol/mol)	Excreted Calcium (mmol/liter)	Sodium/ Creatinine (mol/mol)	Excreted Sodium (mmol/liter)
Patients with Tumors (grouped by primary site of malignancy)										
Pretreatment										
Myeloma	10 (10)	3.36	38.3	308	10	0.47	1.50	0.404	23.9	6.87
		0.13	2.1	65		0.09	0.29	0.095	5.5	2.08
Breast	50 (48)	3.59	33.6	127	36	0.71	1.71	0.225	17.8	2.22
		0.07	0.9	8		0.05	0.16	0.027	3.6	0.50
Head and neck	10 (6)	3.33	31.5	112	10	0.53	1.19	0.131	37.1	4.00
		0.10	1.9	10		0.04	0.21	0.025	12.1	1.38
Miscellaneous	27 (17)	3.68	33.0	143	17	0.59	1.39	0.176	17.7	1.70
		0.09	1.2	20		0.04	0.19	0.031	4.3	0.30
Lung	25 (10)	3.36	31.4	110	14	0.52	1.64	0.069	14.8	1.28
		0.07	0.9	8		0.05	0.18	0.023	3.7	0.28
Kidney	10 (5)	3.35	35.5	107	7	0.52	1.30	0.120	19.6	1.79
		0.06	1.9	15		0.08	0.44	0.029	11.3	0.80
All	132 (96)	3.51	33.5	136	94	0.60	1.53	0.209	18.7	2.64
		0.04	0.5	9		0.03	0.09	0.018	2.4	0.37
Post-treatment										
Myeloma		2.18	36.1	196	10	0.32	0.29	0.048	30.4	5.26
		0.04	1.6	51		0.05	0.06	0.010	3.6	0.86
Breast		2.35	31.2	93	41	0.65	0.30	0.026	19.9	1.73
		0.02	0.9	5		0.04	0.04	0.003	2.5	0.22
Head and neck		2.31	27.0	93	10	0.60	0.28	0.026	18.4	1.74
		0.05	1.7	5		0.05	0.04	0.004	2.9	0.30
Miscellaneous		2.44	30.7	102	25	0.67	0.30	0.028	20.8	2.17
		0.03	1.0	14		0.07	0.09	0.004	2.6	0.33
Lung		2.49	30.3	87	19	0.50	0.35	0.029	21.9	1.89
		0.04	1.4	5		0.04	0.05	0.004	3.0	0.28
Kidney		2.50	33.7	81	10	0.54	0.39	0.030	25.7	1.99
		0.06	1.5	8		0.05	0.13	0.009	3.7	0.27
All		2.39	31.3	100	115	0.64	0.32	0.032	23.8	2.20
		0.02	0.4	6		0.03	0.02	0.002	1.3	0.19
Control Subjects										
Healthy persons										
Fasting	8	2.32	44.0	77	8	1.10	0.19	0.015	15.2	1.10
	8	0.02	0.2	4		0.07	0.03	0.002	2.3	0.12
Calcium-loaded	8	2.44	44.5	73	8	1.53	0.85	0.063	27.1	1.96
		0.02	0.2	3		0.10	0.14	0.010	4.7	0.33
Patients with familial benign hypercalcemia										
Fasting	12	2.84	42.3	63	12	0.84	0.29	0.019	13.7	0.87
		0.03	0.3	2		0.03	0.06	0.004	1.6	0.12
Calcium-loaded	11	2.97	43.2	59	11	1.13	0.87	0.051	28.3	1.65
		0.02	0.4	2		0.08	0.14	0.009	3.2	0.16
Patients with primary hyperparathyroidism	12	2.80	43.3	86	12	0.53	0.63	0.050	11.9	1.04
		0.04	0.6	5		0.03	0.06	0.006	1.3	0.15
Normal values		2.25–2.56	40–48	<100		0.80–1.30	<0.60	<0.060	5–20	0.5–2.0

* Number of patients with bone involvement in parentheses.
† Number of patients for whom urine values were available.
‡ Maximal tubular phosphate reabsorption capacity/glomerular filtration rate.

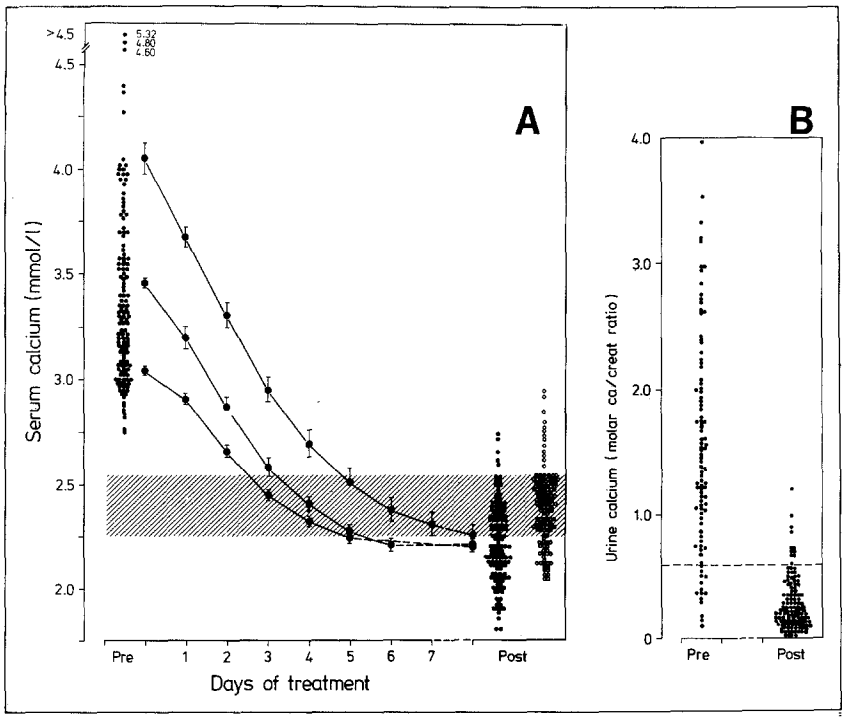

Figure 1. ***A,*** *serum calcium before and after treatment with APD in 132 patients with tumor-induced hypercalcemia.* ***Solid circles*** *indicate the total serum calcium values, and* ***open circles*** *indicate calcium values after correction for serum albumin. The normal range is indicated by the* ***shaded area.*** *The curves represent averages of serum calcium (mean ± SEM) during treatment after division into three groups according to their pretreatment serum calcium level (<3.25, n = 61; >3.75, n = 25; the remainder, n = 46).* ***B,*** *molar urinary calcium/creatinine ratio in the same patients before and after treatment. The* ***broken line*** *is the upper limit of normal.*

RESULTS

Individual values of serum calcium are shown in **Figure 1A** for the patients with tumors. Averages of all biochemical values for all patients are given in Table I, where the patients with tumors have been grouped according to the primary site of malignancy. The table shows that bone involvement was present in most patients with breast cancer and myeloma, but was significantly less in patients with other malignancies. The average serum albumin level was below normal in the tumor patients. The serum creatinine level was increased in all tumor groups, and excessively so in myeloma. Tubular reabsorption of phosphate was significantly decreased in all patients with tumors. The molar sodium/creatinine ratio in the urine was quite high in some patients, reflecting the use of saline infusion in tumor-induced hypercalcemia. The average molar calcium/creatinine ratio in the urine was more than twice the upper limit of normal in all tumor groups, but more than 10 percent of the individual values were within the normal range (**Figure 1B**).

The mean serum calcium values in patients with primary hyperparathyroidism and in patients with familial benign hypercalcemia were lower than in those with tumor-induced hypercalcemia, and serum creatinine values were not abnormally increased. Mean calcium excretion was at the upper limits of normal in patients with primary hyperparathyroidism, whereas it was normal in patients with familial benign hypercalcemia and in control subjects. Calcium administration in normal subjects and in patients with familial benign hypercalcemia caused a significant ($p < 0.01$) increase in serum calcium concentration, tubular phosphate reabsorption, and urine calcium and sodium values.

Institution of treatment was followed by rapid normalization of the serum calcium level in most tumor patients (Table I, Figure 1A). Post-treatment serum calcium values were often low, but clustered in the normal range after correction for the low serum albumin values. Despite normalization of calcium excretion, slight hypercalcemia persisted in 13 patients (10 percent), three with hypernephroma, five with squamous cell lung cancer, two with bladder cancer, two with breast cancer, and one with endometrial cancer. The mean post-treatment calcium concentration was slightly, but significantly, higher than average in the patients with lung and renal tumors ($p < 0.05$) and lower in patients with myeloma ($p < 0.001$). Median time to normalization was between three and four days. The pretreatment serum calcium value was a major determinant of this duration since higher initial values took significantly longer to normalize ($r = 0.70$, $p < 0.001$, $n = 127$).

The results in Table I and Figure 1B show that normalization of the serum calcium concentration was accompanied by a decrease in urine calcium to low values. Normalization of the serum calcium concentration was also associated with obvious improvement in the glomerular filtration rate. On the other hand, the post-treatment tubular phosphate reabsorption values were unchanged and remained low. This contrasts with a significant de-

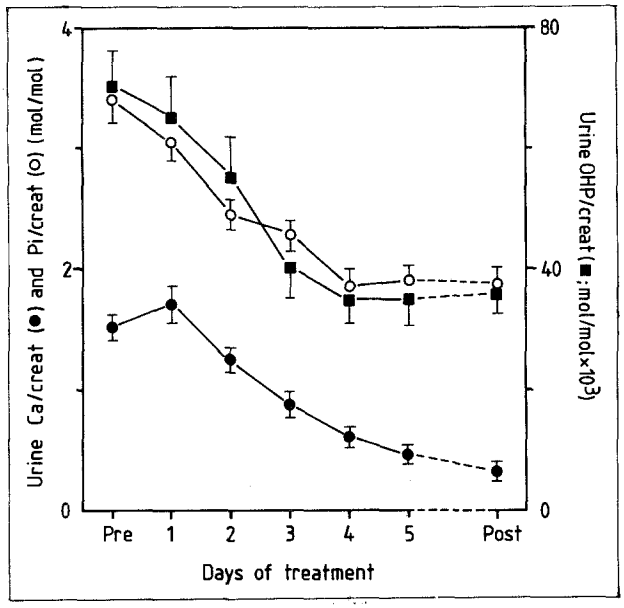

Figure 2. *The effect of treatment on the urinary excretion of calcium (n = 85), phosphate (n = 83), and hydroxyproline (n = 28). Results (mean ± SEM) pertain to patients for whom sequential data were complete.*

crease in urinary phosphate excretion, shown in **Figure 2,** parallel with a decrease in urine calcium and hydroxyproline. The average serum phosphate concentration in all patients also decreased from 1.06 ± 0.34 (SD) mmol/liter before treatment to 0.69 ± 0.23 mmol/liter after treatment, apparently not as a result of a change in renal tubular handling but through the combined effects of an improved glomerular filtration rate and a reduction in the generation of phosphate from bone. There were no significant changes in body temperature or in the number of peripheral leukocytes and lymphocytes during treatment and no significant differences between pre- and post-treatment values of erythrocyte sedimentation rate, serum alkaline phosphatase, 5′-nucleotidase, gamma-glutamyl transpeptidase, or lactic dehydrogenase, nor were other untoward reactions reported.

The results of a retrospective analysis of the effect of sodium administration on sodium and calcium excretion are shown in **Figure 3.** As expected and shown in the inset portion of the figure, patients who were not given additional intravenous saline solution maintained a low average sodium excretion throughout the study, whereas in those in whom saline infusions had been given before and during the study, the average excretion was elevated throughout. In the third group, delay of saline infusion until the start of APD administration occasioned a shift from initially low to later high sodium excretion values. The figure demonstrates that the ability to excrete calcium in chronic hypercalcemia is strongly modified by the requirements of renal sodium transport. For comparison, the figure contains a shaded area indicating reported values for excreted calcium in healthy persons receiving a short-term calcium infusion [15]. The hypercalcemic patients with tumors excreted a smaller fraction of a given filtered calcium load than the healthy subjects, and the difference is most pronounced when sodium excretion is low.

The combined effects of serum calcium concentration (SeCa) and urinary sodium excretion (NaE) on urinary calcium excretion (CaE) in tumor-induced hypercalcemia were quantified by means of a multiple regression analysis of all 787 clearance results obtained before, during, and immediately after treatment. None of the variables appeared to be normally distributed, but the distribution became normal after logarithmic transformation. The analysis gave a partial correlation of 58 percent between ln CaE and ln SeCa and 50 percent between ln CaE and ln NaE and a multiple regression coefficient of 76 percent, whereas sodium excretion and serum calcium concentration were not correlated (1 percent). The multiple regression equation gave ln CaE = 3.79 ln SeCa + 0.48 ln NaE − 3.37.

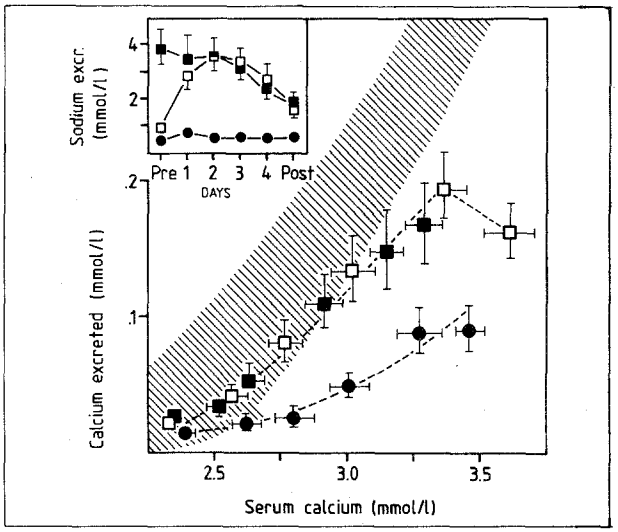

Figure 3. *The relation of excreted calcium to serum calcium during treatment with APD in patients not receiving intravenous sodium chloride treatment (**solid circles**) and in patients receiving more than 1 liter of saline solution daily (**squares**). Patients who had been receiving sodium chloride before and during APD treatment are represented by **solid squares;** patients in whom both treatments were started at the same time are indicated by **open squares** (see Patients and Methods). The mean pretreatment values are those on the right side, the means for the next four days follow leftwards, and the lowest values on the left represent the post-treatment means. The mean excreted sodium values in the same patients and on the same days are depicted in the inset. The symbols represent geometric means ± SEM. The **shaded area** is the range found in healthy persons receiving rapid calcium infusions [15]. The **broken lines** contrast the relations observed in the present study.*

TABLE II Excreted Calcium as Function of Serum Calcium and Excreted Sodium in 125 Patients with Tumor-Induced Hypercalcemia (787 observations) Divided by Indicated Intervals of Serum Calcium (columns) and Excreted Sodium (rows)

Excreted Sodium		Serum Calcium x̄ c.v.											
		<2.25		2.25-<2.50		2.50-<3.00		3.00-<3.50		≥3.50		Total	
x̄	c.v.	2.13	1.01	2.37	1.01	2.71	1.01	3.23	1.01	3.91	1.01	2.75	1.01
<1		0.009	1.27	0.011	1.22	0.024	1.13	0.069	1.12	0.120	1.18	0.030	1.10
0.35	1.07	(16)		(34)		(75)		(45)		(21)		(191)	
1–<2		0.023	1.14	0.032	1.10	0.033	1.06	0.097	1.13	0.222	1.40	0.045	1.08
1.46	1.02	(17)		(38)		(59)		(37)		(10)		(161)	
2–<3		0.023	1.16	0.034	1.12	0.053	1.12	0.146	1.15	0.238	1.13	0.052	1.09
2.46	1.01	(21)		(39)		(53)		(19)		(8)		(140)	
3–<4		0.033	1.26	0.045	1.13	0.073	1.17	0.161	1.19	0.207	1.54	0.071	1.11
3.42	1.01	(13)		(21)		(23)		(17)		(4)		(78)	
4–<6		0.042	1.17	0.051	1.17	0.120	1.10	0.182	1.11	0.322	1.10	0.099	1.02
4.81	1.01	(15)		(24)		(33)		(16)		(10)		(98)	
≥6		0.062	1.22	0.090	1.30	0.163	1.09	0.317	1.14	0.497	1.13	0.212	1.09
9.71	1.12	(6)		(17)		(40)		(34)		(22)		(119)	
Total		0.024	1.10	0.033	1.08	0.052	1.07	0.131	1.07	0.250	1.11	0.061	1.04
1.90	1.05	(88)		(173)		(283)		(168)		(75)		(787)	

Values represent geometric means (x̄ in mmol/liter) and coefficients of variation (c.v.); numbers in partentheses indicate numbers of observations.

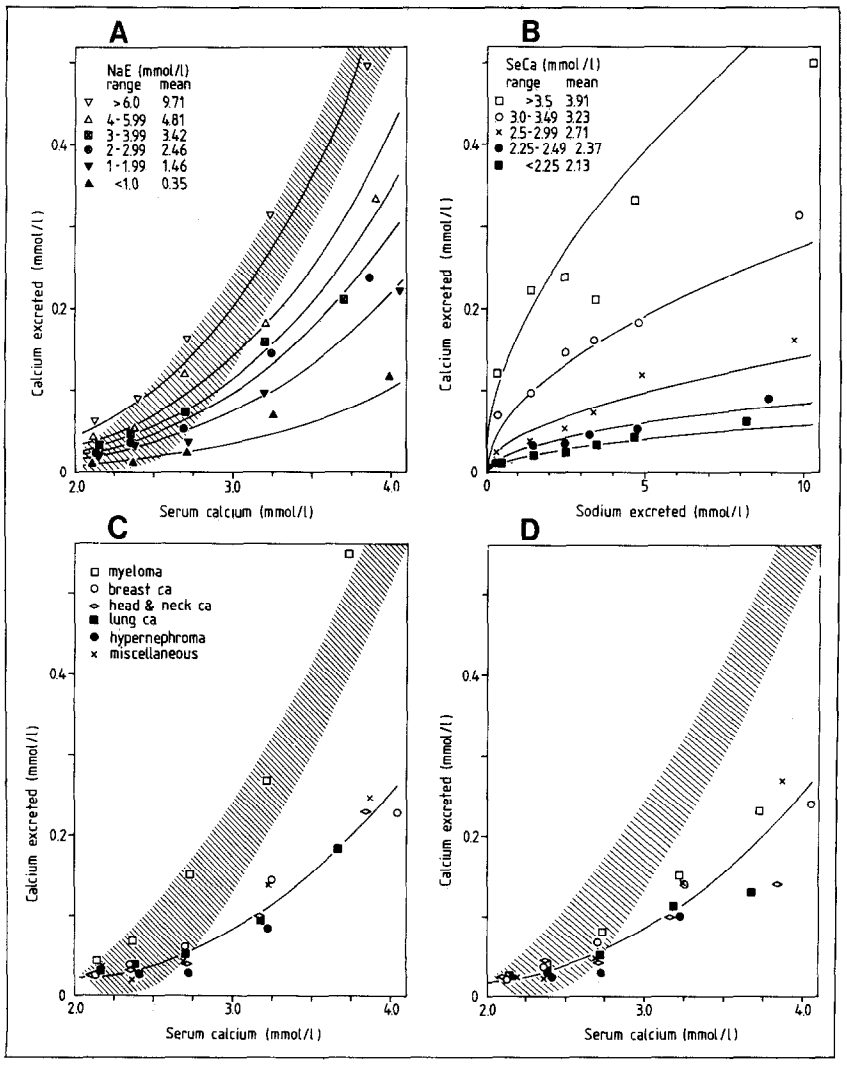

Figure 4. *The influence of excreted sodium on the relation of excreted calcium to serum calcium (**panel A**) and the influence of serum calcium on the relation between excreted calcium and excreted sodium (**panel B**) during treatment with APD in tumor patients. The curves depict the relationship for the intervals of excreted sodium and serum calcium as indicated in the upper left corner of the panels and according to the multiple regression equation described in the text. The points are the averages from Table II. **Panel C** shows the relation between excreted calcium and serum calcium for the same patients, grouped according to the primary site of malignancy as indicated by the six symbols. The values for excreted calcium are geometric means according to the subsequent intervals of serum calcium shown in **panel B.** The results in **panel D** were obtained in the same manner but after prior factorization of excreted calcium for excreted sodium. The technique of factorization is described in the text and uses the average of excreted sodium (1.9 mmol/liter, see Table II) as a basis. The calculated relationship of excreted calcium to serum calcium for this average is shown by the curves in panels C and D. The **shaded area** in panels A, C, and D corresponds with that in Figure 3.*

In **Table II** the data-sets are organized into 30 blocks, according to intervals of serum calcium and of excreted sodium. The means pertaining to the 30 blocks were used to obtain the equation of the form $\ln CaE = 3.86 \ln SeCa + 0.54 \ln NaE - 7.06$. The partial correlation coefficients were found to be 81 percent for serum calcium and 55 percent for excreted sodium, and the multiple correlation coefficient was 98.6 percent. This value is sufficiently large to use the equation for prediction of average excreted calcium values at given levels of serum calcium and excreted sodium. The curves in **Figures 4A** and **4B** depict this relationship, the points representing the averages from Table II. Figure 4A shows that the increase in calcium excretion for a given rise in serum calcium concentration is smaller, the lower the excreted sodium value. Figure 4B shows that the influence of sodium excretion on calcium excretion is larger, the higher the serum calcium concentration.

The same multiple regression equation was used to eliminate the effect of variations of excreted sodium on the observed relation between calcium excretion and serum calcium concentration. Actual values of calcium excretion were multiplied by $(1.9/NaE)^{0.54}$, where 1.9 represents the mean for sodium excretion in all data. With this value, a curve was obtained, which is compared in **Figures 4C** and **4D** with the so-called "normal relationship" [15]. Mean values of calcium excretion for individual tumor groups are compared with the overall average before (Figure 4C) and after (Figure 4D) sodium excretion has been taken into account. The figure shows that patients with myeloma behave more "normally" than the others, merely because their low glomerular filtration rate is responsible for a high sodium excretion per unit volume of glomerular filtrate. In addition to this, Figure 4D shows that the apparent inability of tumor patients to excrete a given load of calcium is more closely related to the degree of hypercalcemia than to the nature of the tumor. Differences in renal calcium excretion between the various tumor groups are further analyzed in **Figure 5.** This gives all 787 observations after normalization to the overall averages of excreted sodium (1.9 mmol/liter) and serum calcium (2.75 mmol/liter) during treatment and arranged according to the site of the malignancy. The actual values of calcium excretion were multiplied by $(1.9/NaE)^{0.54} \cdot (2.75/SeCa)^{3.86}$. The range of the factorized values for calcium excretion is the same in each tumor group. However, the fraction of values in the lower range is significantly larger in patients with hypernephroma than in all others. It is also significantly smaller in patients with breast carcinoma and myeloma with respect to all other malignancies.

The multiple regression equation, which so closely defines the relation between excreted calcium as the dependent variable on the one hand and serum calcium and excreted sodium on the other, is used in **Table III** to define the deviation of a given value from this relationship

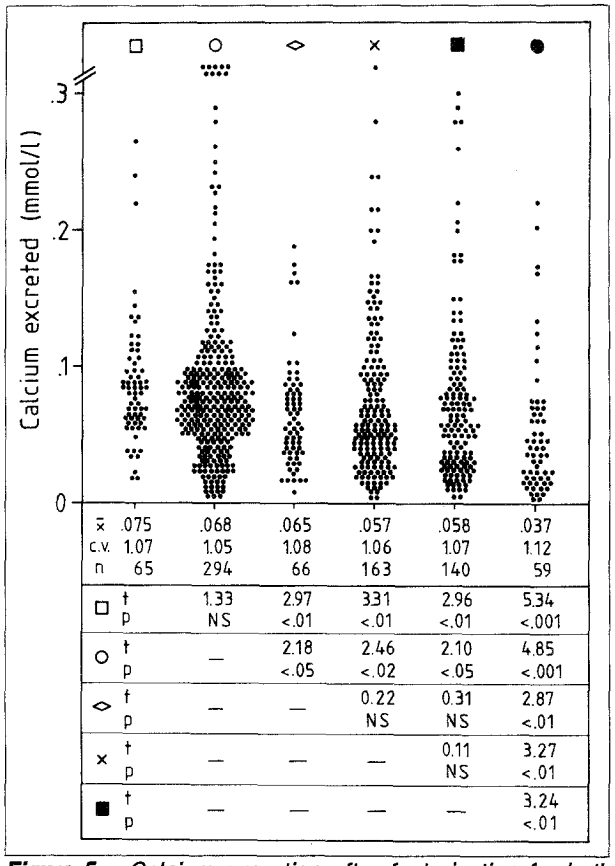

Figure 5. *Calcium excretion after factorization for both the overall average of excreted sodium (1.9 mmol/liter) and serum calcium (2.75 mmol/liter). Results pertain to 787 observations in 125 patients, grouped on the basis of the primary site of the malignancy as indicated by the symbols (as in Figure 4C). Geometric means for excreted calcium are shown numerically ($\bar{x}$ = geometric mean; c.v. = coefficient of variation; n = number of observations), and the results from which the means were derived are shown as* ***solid circles.*** *The significance of differences between the means of the six different tumor groups is indicated with the respective t and p values.*

for the tumor patients after treatment and to compare the results with those in other hypercalcemic conditions: calcium-loaded healthy persons and patients with familial benign hypercalcemia and primary hyperparathyroidism. There was no significant difference between the majority of patients with tumors, calcium-loaded healthy subjects, and patients with primary hyperparathyroidism. Calcium excretion was, however, low in fasting normal subjects and in patients with familial benign hypercalcemia and remained relatively low in those groups of tumor patients who also had low values during treatment.

COMMENTS

Most hypercalcemic patients with tumors exhibited hypercalciuria, whatever the nature of the primary tumor. Both hypercalcemia and hypercalciuria resolved through inhibi-

TABLE III Comparison of Post-Treatment Renal Calcium Handling in Patients with Tumor-Induced Hypercalcemia and Calcium Handling in Untreated Patients with Primary Hyperparathyroidism and in Patients with Familial Benign Hypercalcemia and Healthy Persons when Fasting and after Oral Calcium Loading

	Number	Actual/Derived Excreted Calcium*
Patients with tumors		
Myeloma	10	1.07 ± 0.15
Breast	41	0.96 ± 0.09
Head and neck	10	0.98 ± 0.15
Miscellaneous	25	0.77 ± 0.11
Lung	19	0.79 ± 0.09
Kidney	10	0.73 ± 0.17
All	115	0.88 ± 0.05
Control subjects		
Healthy subjects	8	
Fasting		0.65 ± 0.11
Calcium-loaded		1.60 ± 0.11
Patients with familial benign hypercalcemia		
Fasting	12	0.42 ± 0.07
Calcium-loaded	11	0.68 ± 0.12
Patients with primary hyperparathyroidism	12	1.20 ± 0.13

* These figures are means ± SEM for measured values divided by values derived from serum calcium and excreted sodium according to the multiple regression equation.

tion of bone resorption with APD, as shown by the concomitant reductions in the excretion of calcium, phosphate, and hydroxyproline—three typical constituents of mineralized bone matrix. This confirms that excessive bone resorption was a major component of tumor-induced hypercalcemia, although no local bone invasion could be demonstrated in a sizeable proportion of the patients. Malignancies can increase bone resorption through local actions, but it is also accepted that tumors outside the skeleton can produce humoral factors that cause generalized and osteoclastic resorption of bone [12,27–29]. The present prospective study, however, does not merely confirm the efficacy of inhibition of bone resorption by bisphosphonate in tumor-induced hypercalcemia [2–11], it also establishes the predictability, safety, and usefulness of APD in a variety of malignant conditions.

Despite the skeletal origin of the hypercalcemia, there was a definite renal contribution to its maintenance. Not all patients had an abnormally high urine calcium/creatinine ratio when untreated, and not all treated patients, in whom a previously elevated ratio had normalized, had an entirely normal serum calcium concentration after treatment. Hypercalcemia reduces the glomerular filtration rate [13,14]. This and the beneficial effect on the glomerular filtration rate of normalization of the serum calcium concentration are herein confirmed. It has been suggested that renal tubular calcium transport is also abnormal in hypercalcemic tumor patients [9,11,16–18], but this has been difficult to establish, because the effects of variations in salt intake on renal calcium transport have been insufficiently studied.

The pivotal element of the present study is the result of a decision to let the sodium chloride treatment vary. In retrospect, this generated data in which great variability of sodium excretion is combined with a wide range of serum calcium values. This allowed analysis of the combined effects of serum calcium concentration, renal sodium handling, and tumor type on the excreted calcium in tumor-induced hypercalcemia. The data show that renal sodium retention in tumor patients was not excessive, in that sodium excretion was considerable in some patients and followed the presumed variations in saline infusion. The data also demonstrate that, for a given serum calcium value, the excretion of calcium depends upon the excretion of sodium. This adaptation is achieved, at least for a significant part, at transport sites that subserve the combined renal tubular resorption of calcium and sodium. Normally, 60 to 80 percent of the filtered calcium load is resorbed together with sodium in the more proximal regions of the renal tubules [30]. Sodium-independent resorption of calcium, which is regulated by parathyroid hormone, occurs in far distal tubular regions. The latter would be expected to be suppressed in tumor-induced hypercalcemia, leaving a larger fraction of the totality of renal tubular calcium transport dependent upon volume regulation.

The major problem with interpretation of such data is created by comparison with reference values, derived from short-term calcium infusion studies in healthy persons [15]. We show herein that the use of these reference values is inappropriate. Short-term calcium loading in healthy persons appears to induce considerable urinary sodium excretion. This sodium diuretic effect of calcium infusion has been well established [19,20]. Therefore, persons who receive short-term calcium loads are not in a steady state with respect to sodium but will demonstrate progressive sodium loss as long as the requirements of sodium homeostasis are not met through compensatory stimulation of sodium resorptive mechanisms. The data suggest that re-establishment of sodium balance in chronically hypercalcemic patients is achieved through stimulation of sodium resorption in the proximal tubules, where this is linked with the resorption of calcium. This apparent increase in tubular reabsorption of calcium in tumor-induced hypercalcemia in response to a sodium diuretic effect of calcium resembles the action of thiazides. Thiazide diuretics also induce a steady state in which calcium clearance is reduced relative to sodium clearance, while

sodium excretion adapts to variation of sodium intake, in the presence of reduced extracellular volume [31,32]. In prolonged hypercalcemia, as opposed to acute hypercalcemia, sodium homeostasis takes precedence over calcium homeostasis. We have described the resulting altered relation between excreted calcium, serum calcium, and excreted sodium with a multiple regression equation, which allowed us to investigate the effect of tumor type on calcium transport. The results of this analysis are the first evidence of inappropriately high, sodium-independent calcium reabsorption in patients with certain types of tumors and thus support the assumption that such tumors can produce substances with a parathyroid hormone-like effect on the renal tubular handling of calcium [10,11, 16–18,33,34]. The conditions in which this occurred with the greatest frequency were hypernephroma and lung cancer, which are tumors with the lowest incidence of bone metastases.

It was interesting that calcium excretion in fasting healthy persons was lower than predicted by the equation. This result could be expected because tumor-induced hypercalcemia suppresses the production of parathyroid hormone [35] and, therefore, reduces sodium-independent calcium resorption in the more distal nephron sites. It was surprising, however, that there was no clear evidence of increased renal tubular resorption of calcium in primary hyperparathyroidism. Obviously this result requires further investigation. It is furthermore noteworthy that sodium-independent calcium resorption was confirmed to be increased in familial benign hypercalcemia with or without calcium loading [23].

The failure of the tubular phosphate reabsorption to normalize after treatment was striking. The decrease of phosphate resorption in these patients can be attributed to tumor-derived factors; although it occurs rarely as an isolated phenomenon in malignant tumors, it is frequent in tumor-induced hypercalcemia [16,17,28]. It should, however, be remembered that, although acute hypercalcemia is associated with a rise in tubular phosphate resorption (Table I), chronic hypercalcemia may lower it; moreover, greatly delayed recovery of normal phosphate resorption capacity has, for instance, been observed after treatment of vitamin D intoxication [36].

We conclude that the ability of the kidney to deal with an increased filtered load of calcium through augmentation of fractional calcium excretion is reduced in tumor-induced hypercalcemia. Tumor-derived humoral factors contribute to this reduction, but the major limitation to the excretion of calcium is occasioned by an augmentation of calcium-associated sodium reabsorption capacity, which compensates for the sodium diuretic effect of a high calcium concentration in the glomerular filtrate. Therefore, effective treatment not only should aim at reversing the increased generation of calcium from bone but also requires intravenous administration of sodium chloride for as long as the hypercalcemia persists.

ACKNOWLEDGMENT

We thank Mrs. H. E. Stuivenberg-Bleijswijk for secretarial assistance and Drs. M. A. Nooy, K. J. Roozendaal, P. J. Kulberg, and H. van Slooten for entering patients into this study. APD was kindly donated by Henkel K GaA, Düsseldorf, West Germany. APD for intravenous use is currently under clinical investigation at Ciba-Geigy, Basel, Switzerland, with the code CGP-23339.

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