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Urological Research

Biochemical Changes Before and During Oral Calcium Tolerance Test in Calcium Stone Formers

T. Kitamura[1], Y. Hirano[2], D. Ueda[3], and Y. Aso[2]

[1] Department of Urology, Branch Hospital, Faculty of Medicine, University of Tokyo, Tokyo, Japan
[2] Department of Urology, Faculty of Medicine, University of Tokyo, Tokyo, Japan
[3] Department of Urology, Yaizu General Hospital, Yaizu, Japan

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Summary. 116 normocalcemic and 8 primary hyperparathyroid (PHPT) patients with calcium (Ca) nephrolithiasis and 10 normal controls underwent 1 g of oral Ca tolerance test following 4 days of Ca restricted diet (400 mg/day). On the basis of urinary Ca/creatinine (Cr) ratio obtained by the test, the 116 patients with normocalcemic nephrolithiasis were divided into 3 groups (normocalciuric nephrolithiasis; NN, absorptive hypercalciuria; AH, renal hypercalciuria; RH) according to our criteria which were slightly modified from Pak et al. Changes in urinary Ca/Cr ratio, and those in serum Ca and phosphorus (P), tubular maximum reabsorption of phosphate/glomerular filtration rate ($TmPO_4$/GFR), nephrogenous adenosine 3′,5′-monophosphate (NcAMP) and plasma immunoreactive parathyroid hormone (iPTH) were determined. As a result, the 116 patients were divided into 82NN, 13AH and 21RH. In general, a rise in serum Ca and fall in NcAMP were seen first, followed by rises in urinary Ca/Cr ratio, serum P and $TmPO_4$/GFR although the changes were small. The group PHPT showed abnormality in the changes of $TmPO_4$/GFR, NcAMP and plasma iPTH. The former one decreased constantly during the test and the latter two did not fall to within the normal range, suggesting parathyroid autonomy or abnormal suppressibility. Regarding the normal controls, all the changes were smallest among the 5 groups and clear parathyroid suppression was not observed while it was seen in the groups NN, AH and RH. In conclusion, oral Ca tolerance test is useful not only to separate NN, AH and RH, but also for the diagnosis of PHPT by demonstrating parathyroid autonomy or abnormal suppressibility assessed by NcAMP and/or $TmPO_4$/GFR.

Key words: Oral calcium load – Calcium nephrolithiasis – Nephrogenous cyclic AMP – Parathyroid hormone – Phosphate threshold

Introduction

Intraveous calcium (Ca) infusion test was introduced by Howard et al. [6] in 1953 as a parathyroid suppression test. It was developed mainly for the purpose of differentiating hyperparathyroid patients from euparathyroid individuals by detecting no significant reduction in urinary phosphorus (P) excretion in spite of the raised serum Ca level, which is based on the hypothesis [6] of parathyroid autonomy in primary hyperparathyroidism (PHPT). However, it is recognized that true autonomy can be confused with abnormal suppressibility [2] and that diagnosis of PHPT depending on urinary P excretion alone is not reliable. Thus, the intravenous Ca infusion test became less useful for differentiating PHPT from normal although it remains valid for suppression of parathyroid activity.

The oral Ca tolerance test has been used to discriminate the two forms of idiopathic hypercalciuria; one is absorptive hypercalciuria (AH), which is due to primary hyperabsorption of Ca from the intestine, and the other is renal hypercalciuria (RH) which is due to primary renal leak of Ca, by Pak et al. [10]. The oral test is particularly useful because orally administered Ca is absorbed from the intestine and excreted in the urine, so that the absorbed amount of Ca can be estimated from the urinary excretion. Therefore, the oral Ca tolerance test will be more suitable for differentiating AH from RH. Moreover, the method is simple and safe.

Parathyroid suppressibility in normal subjects in patients with Ca-containing nephrolithiasis and in PHPT patients assessed by the oral Ca tolerance test has been reported by a limited number of investigators [3, 4, 9, 11, 12]. It has been demonstrated that parathyroid function during the oral Ca tolerance test assessed by nephrogenous adenosine 3′,5′-monophosphate (NcAMP) and plasma immunoreactive parathyroid hormone (iPTH) is slightly suppressed in normal subjects, normocalciuric nephrolithiasis (NN) and AH, and moderately suppressed in RH, while it is not suppressed or showed abnormal suppressibility in PHPT.

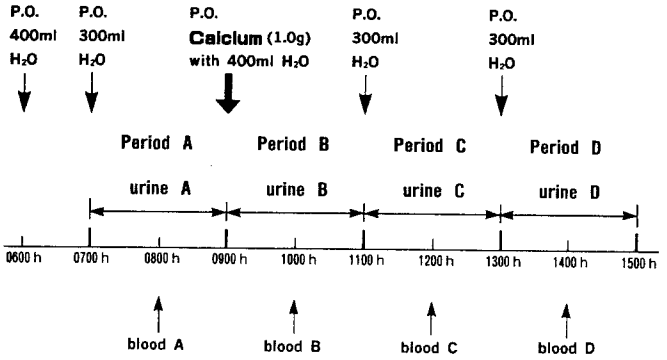

Fig. 1. Protocol for oral calcium tolerance test. A calcium restricted diet (Ca 400 mg/day, P 700 mg/day, NaCl 3 g/day and approximately 1,500 calories/day) is given for 4 successive days prior to the test. P.O. = per os

Recently, we examined biochemical changes before and during oral Ca tolerance test in 124 patients with Ca-containing nephrolithiasis including 8 PHPT patients, and obtained slight parathyroid suppression in stone formers (SF), and parathyroid autonomy or abnormal suppressibility in PHPT patients.

Subjects and Methods

Subjects

Ten healthy volunteers and 124 patients with Ca nephrolithiasis underwent oral Ca tolerance test. Some of the data from 10 healthy volunteers were previously reported [8].

Of the 124 patients, 15 were newly added to the 109 patients reported previously [8]. Of the 15 patients, 2 were diagnosed as having PHPT and the remainder as having normocalcemic nephrolithiasis after thorough clinical and biochemical evaluation. Subsequently, the 2 patients were proven to have a parathyroid adenoma following a neck exploration. All the clinical settings about normal controls and patients are the same as the previous report [8].

Study Protocol

Informed consent was obtained from every individual tested and all medications were withheld during at least 1 week before the study. The study protocol for oral Ca tolerance test was described earlier [8] and was as follows:

Prior to the test, all patients and normal controls were admitted to hospital and placed on a Ca-restricted diet (Ca 400 mg/day, P 700 mg/day, NaCl 3 g/day and approximately 1,500 calories/day) for 4 days drinking only distilled water (H_2O). This regimen of Ca-restricted diet is slightly modified from Pak et al. [11]. On the 5th day, after an overnight fast, the oral Ca tolerance test was performed with sufficient hydration from 7:00 a.m. through 3:00 p.m. while fasting continued. As shown in Fig. 1, a 2-hour urine sample from 7:00 a.m. to 9:00 a.m. was collected for the basal level (period A). At 9:00 a.m. 1 g of Ca (11.19 g of Ca gluconate dissolved in 400 ml of hot H_2O) was administered orally after the solution was cooled to room temperature and 3 additional 2-hour urine samples were collected for periods B, C and D. At the midpoint of each 2-hour urine collection period a blood sample was drawn for determination of serum Ca, P and Cr, and plasma adenosine 3',5'-monophosphate (cAMP) and iPTH. Urine samples were analyzed for Ca, P, Cr and cAMP. The procedures for processing blood and urine samples were described elsewhere [7].

During the test no serious adverse side effects were observed except for diarrhoea in some of the tested individuals.

Operational Classification for NN, AH and RH

116 patients without PHPT were divided into 3 groups according to a criterion modified from Pak et al. [11]. Our criteria (Table 1), which was described previously [8], for classifying normocalcemic nephrolithiasis is fundamentally based on urinary Ca/Cr ratio(s) before and during the test but not on the amount of daily urinary Ca excretion because some inconsistencies could often be seen between daily urinary Ca excretion and urinary Ca/Cr ratio(s) before and during the test.

Analyses

Plasma and urine cAMP were determined by radioimmunoassay (RIA) using a YAMASA cAMP assay kit (Yamasa, Choshi, Japan). The precise methodology was described elsewhere [7]. The intra-assay and interassay coefficients of variation were 5.0 to 9.5%, respectively. NcAMP was calculated by the formula of Broadus et al. [1] and the normal range was less than 3.33 n mol/100 ml glomerular filtrate (n mol/100 ml GF).

Plasma iPTH was measured by a RIA kit of synthetic human PTH (46–84) (Eiken, Tokyo, Japan), which detected only the carboxy terminal portion of the human PTH molecule and the results were expressed as the equivalent concentration of purified human parathyroid hormone (PTH). The precise methodology was described elsewhere [8]. The intraassay and interassay coefficients of variation were 3.6 and 4.2%, respectively. The normal range was less than 0.5 ngEq/ml.

Table 1. Criteria for classification among calcium-containing urinary stone formers by oral calcium tolerance test (modified from Pak et al. [11])

	Before load urinary Ca/Cr (mg Ca/mg Cr)	After load urinary Ca/Cr (mg Ca/mg Cr)
Normocalciuric nephrolithiasis (NN)	< 0.11	< 0.2
Absorptive hypercalciuria (AH)	< 0.11	$\geqq 0.2$
Renal hypercalciuria (RH)	$\geqq 0.11$	any value

(normocalcemia in every group)

Table 2. Clinical data for each group (mean ± SD)

Group	*n*	Age (years)	Weight (kg)	Mode of nephrolithiasis	
				(single SF)	(MSF and/or RSF)
NN					
Total	82	41.2 ± 13.2	61.0 ± 8.7	36	46
Males	64	41.0 ± 13.6	62.9 ± 8.6	27	37
Females	18	42.1 ± 12.3	54.1 ± 5.0	9	9
AH					
Total	13	41.7 ± 13.5	56.4 ± 8.8	4	9
Males	9	42.4 ± 10.2	58.0 ± 8.6	3	6
Females	4	40.0 ± 21.2	53.0 ± 9.2	1	3
RH					
Total	21	42.4 ± 15.3	52.3 ± 8.6	9	12
Males	9	37.7 ± 7.8	59.6 ± 5.9	3	6
Females	12	45.9 ± 18.7	46.9 ± 5.9	6	6
PHPT					
Total	8	44.3 ± 16.4	52.9 ± 7.3	4	4
Males	2	45.0 ± 35.4	50.5 ± 9.2	1	1
Females	6	44.0 ± 11.3	53.7 ± 7.4	3	3
Normal controls					
Total	10	27.8 ± 8.4	56.6 ± 10.5	–	–
Males	7	27.0 ± 8.9	59.9 ± 10.3	–	–
Females	3	29.7 ± 8.4	49.0 ± 7.0	–	–

SF = Stone formers; MSF = multiple stone formers; RSF = recurrent stone formers; NN = normocalciuric nephrolithiasis; AH = absorptive hypercalciuria; RH = renal hypercalciuria; PHPT = primary hyperparathyroidism

The Ca, P and Cr levels in serum and urine were determined by an autoanalyzer. $TmPO_4/GFR$ was calculated by the nomogram of Walton and Bijvoet [13] and the normal range was 3.4 ± 0.4 mg/dl.

Statistics

Results were presented as the group mean ± standard deviation (mean ± SD). Comparisons between groups were made by Student's *t* test.

Results

Clinical Characteristics for the 5 Groups

As shown in Table 2, 124 SF were divided into 4 groups according to our criteria slightly modified from Pak et al. [11], and the 5th group was composed of normal controls. The 124 SF consist of 82 patients (66.1% of the 124 SF) with NN, 13 (10.5%) with AH, 21 (16.9%) with RH and 8 (6.5%) with PHPT. About 1/3 of the 124 SF had hypercalciuria when PHPT patients were grouped with the AH and RH patients.

The mean ages of the SF were 40 years, whereas the mean age in the normal controls was 27.8 year. Males were predominant in the groups NN, AH and normal controls, but females predominated in the groups RH and PHPT. The 5 groups had similar body weights. Multiple and/or recurrent SF were more frequent than single SF in the groups NN, AH and RH but not in the group of PHPT.

Biochemical Changes Before and During the Oral Ca Tolerance Test

All data (mean ± SD) and significant differences are listed in Table 3. In each group, there were large overlaps between the levels before and during the test, especially in those of NcAMP, plasma iPTH and $TmPO_4/GFR$. It would be so complicated to depict the results including SD that the figures will be presented with the mean levels and with significant differences at peaks or nadirs.

Mean Urinary Ca/Cr Ratio (Fig. 2)

Each curve formed by the 4 mean urinary Ca/Cr ratios before and during the test shows gradual increase during the first 2 periods and reached its peak at the period C in the all 5 groups with the highest level in the group PHPT follow-

Table 3. Biochemical changes in each group before and during oral calcium tolerance test (mean ± SD)

Group	*n*	Urinary Ca/Cr ratio (mg Ca/mg Cr)				Serum Ca (mg/dl)			
period		A	B	C	D	A	B	C	D
NN	82	0.050 ± 0.020	0.080 ± 0.030[a]	0.120 ± 0.040[a]	0.091 ± 0.035[a]	9.4 ± 0.4	9.9 ± 0.4[a]	9.8 ± 0.4[a]	9.7 ± 0.4[a]
AH	13	0.077 ± 0.026	0.128 ± 0.039[a]	0.231 ± 0.027[a]	0.173 ± 0.037[a]	9.4 ± 0.6	10.2 ± 0.9[c]	10.0 ± 0.6[c]	9.9 ± 0.6[c]
RH	21	0.150 ± 0.037	0.222 ± 0.075[a]	0.279 ± 0.119[a]	0.248 ± 0.108[a]	9.5 ± 0.5	10.1 ± 0.4[a]	10.0 ± 0.5[b]	9.8 ± 0.5
PHPT	8	0.173 ± 0.063	0.227 ± 0.081	0.329 ± 0.103[b]	0.260 ± 0.099	11.3 ± 0.6	12.1 ± 0.7[c]	12.1 ± 0.7[c]	11.9 ± 0.8
Normal	10	0.039 ± 0.016	0.065 ± 0.029[c]	0.084 ± 0.040[b]	0.075 ± 0.041[c]	9.5 ± 0.3	9.9 ± 0.2[b]	9.9 ± 0.4[c]	9.6 ± 0.3
Group	*n*	NcAMP (n mol/100 ml GF)				Plasma iPTH (ng Eq/ml)			
period		A	B	C	D	A	B	C	D
NN	82	1.72 ± 0.61	1.31 ± 0.69[a]	1.54 ± 0.76	1.63 ± 0.76	0.33 ± 0.10	0.32 ± 0.10	0.32 ± 0.11	0.32 ± 0.11
AH	13	1.86 ± 0.51	1.61 ± 0.86	1.82 ± 0.45	1.97 ± 0.76	0.29 ± 0.10	0.29 ± 0.10	0.28 ± 0.10	0.29 ± 0.09
RH	21	2.17 ± 0.75	1.73 ± 0.68	1.88 ± 1.32	1.93 ± 0.84	0.30 ± 0.05	0.29 ± 0.09	0.29 ± 0.09	0.30 ± 0.09
PHPT	8	4.92 ± 1.20	4.20 ± 0.88	4.77 ± 1.11	4.68 ± 1.17	0.48 ± 0.28	0.43 ± 0.26	0.39 ± 0.26	0.45 ± 0.32
Normal	10	1.01 ± 0.67	1.09 ± 0.87	1.05 ± 0.58	1.41 ± 0.74	0.26 ± 0.06	0.27 ± 0.06	0.25 ± 0.07	0.23 ± 0.08
Group	*n*	$TmPO_4/GFR$ (mg/dl)				Serum P (mg/dl)			
period		A	B	C	D	A	B	C	D
NN	82	3.04 ± 0.58	3.23 ± 0.60[c]	3.35 ± 0.64[b]	3.19 ± 0.59	3.3 ± 0.4	3.5 ± 0.5[b]	3.6 ± 0.5[a]	3.6 ± 0.4[a]
AH	13	3.08 ± 0.52	3.26 ± 0.50	3.48 ± 0.57	3.25 ± 0.43	3.4 ± 0.4	3.6 ± 0.5	3.7 ± 0.4	3.6 ± 0.4
RH	21	3.22 ± 0.56	3.43 ± 0.64	3.77 ± 0.78[c]	3.53 ± 0.65	3.6 ± 0.4	3.8 ± 0.5	3.9 ± 0.5[c]	3.8 ± 0.5
PHPT	8	2.03 ± 0.41	2.03 ± 0.32	2.00 ± 0.27	1.88 ± 0.23	2.5 ± 0.3	2.5 ± 0.3	2.6 ± 0.3	2.5 ± 0.3
Normal	10	3.24 ± 0.41	3.41 ± 0.46	3.29 ± 0.44	3.35 ± 0.77	3.4 ± 0.4	3.5 ± 0.4	3.5 ± 0.4	3.5 ± 0.4

[a] $P < 0.001$ vs. period A, [b] $P < 0.01$ vs. period A, [c] $P < 0.05$ vs. period A

A, B, C and D represent 2 h-period before and first, second and third 2 h-period after 1 g of oral calcium load, respectively. Ca = calcium; Cr = creatinine; NcAMP = nephrogenous adenosine 3′,5′-monophosphate; GF = glomerular filtrate; iPTH = immunoreactive parathyroid hormone; $TmPO_4/GFR$ = tubular maximum reabsorption of phosphate/glomerular filtration rate; P = phosphorus

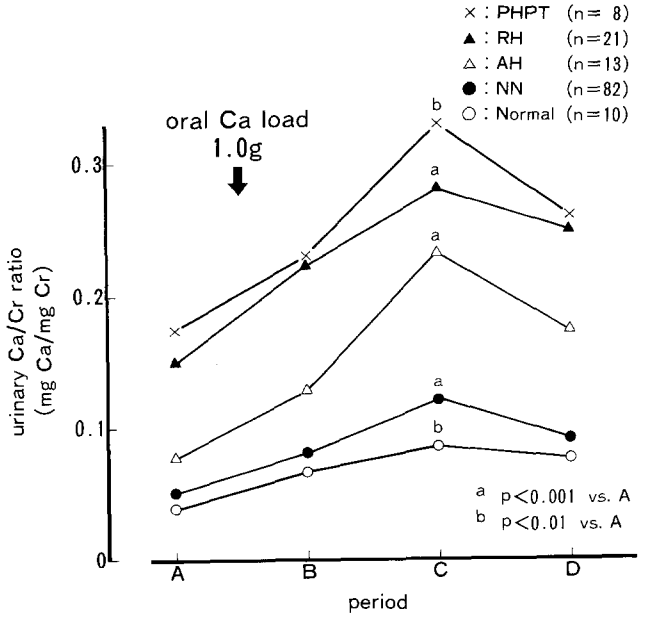

Fig. 2. Changes in mean urinary calcium/creatinine (Ca/Cr) ratio before and during oral calcium tolerance test in the 5 groups. Significant differences at peaks (period C) are presented

ed by the groups RH, AH, NN and normal controls, the mean ratio then fell but not to the basal levels.

The increase (Δ) between the mean urinary Ca/Cr ratios in the periods A and C was highest in the group PHPT (Δ) 0.156 mg Ca/mg Cr, $P < 0.01$) followed by the groups AH (Δ) 0.154 mg Ca/mg Cr, $P < 0.001$), RH (Δ) 0.129 mg Ca/mg Cr, $P < 0.001$), NN (Δ) 0.070 mg Ca/mg Cr, $P < 0.001$) and normal controls (Δ) 0.045 mg Ca/mg Cr, $P < 0.01$).

Mean Serum Ca and P (Fig. 3)

The curve depicted by the 4 mean serum Ca levels before and during the test was sustained in the group PHPT with its peak at the period B ($P < 0.05$, vs. period A), whereas the curves in the remainder were within the normal range and showed their peaks in period B followed by a gradual fall but not to basal levels. Although the increases between the mean serum Ca levels in the periods A and B were not remarkable, the largest ones were 0.8 mg/dl in the groups PHTP ($P < 0.05$) and AH ($P < 0.05$) followed by the groups RH (Δ 0.6 mg/dl, $P < 0.001$), NN (Δ 0.5 mg/dl, $P < 0.001$) and normal controls (Δ 0.4 mg/dl, $P < 0.01$).

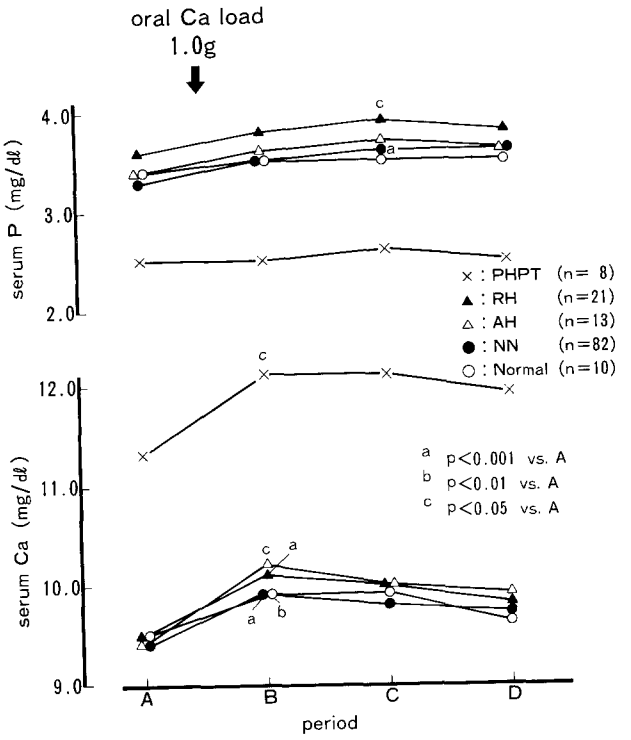

Fig. 3. Changes in mean serum calcium (Ca) and phosphorus (P) before and during oral calcium tolerance test in the 5 groups. Significant differences at peaks (period B for Ca and period C for P) are presented

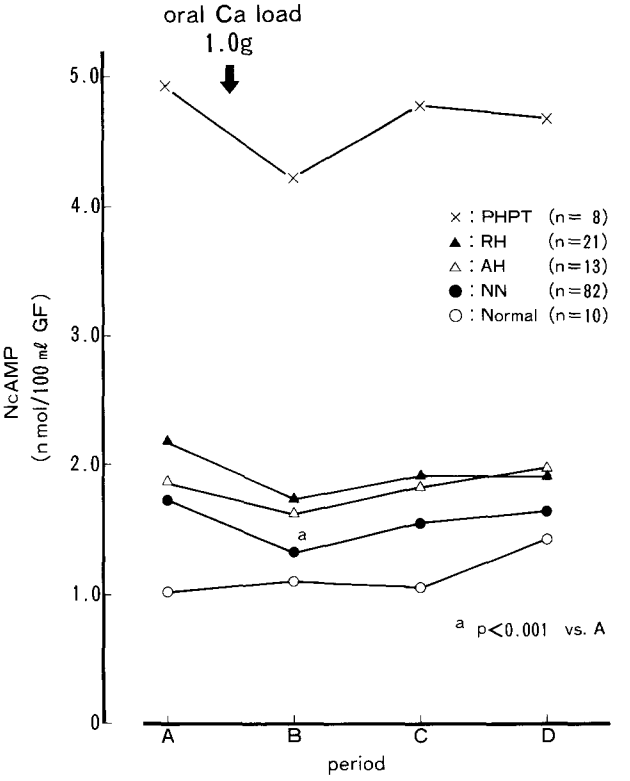

Fig. 5. Changes in mean nephrogenous adenosine 3′,5′-monophosphate (NcAMP) before and during oral calcium tolerance test in the 5 groups. Significant nadir is seen only at period B in the group NN

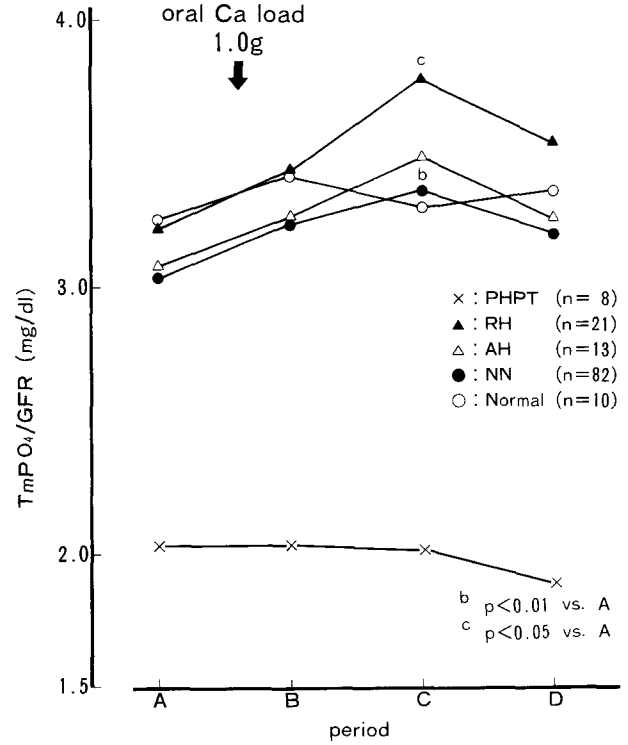

Fig. 4. Changes in mean tubular maximum reabsorption of phosphate/glomerular filtration rate ($TmPO_4/GFR$) before and during oral calcium tolerance test in the 5 groups. Significant differences at peaks (period C) are presented

With regard to the changes in the mean serum P levels, the curve in the group PHPT remained low, while the curves in the remainder were within the normal range. The peaks were observed at the period C in the all groups though the increases between the levels before and during the test were very small (Δ 0.1–0.3 mg/dl) and not significant in the groups AH, PHPT and normal controls.

Mean $TmPO_4/GFR$ (Fig. 4)

The curve in the group PHPT showed a gradual decrease (though not significant) from the basal level to the period D and was sustained at a low level, whereas the curves in the remainder were within the normal range with the peaks at the period C except for the normal controls in which the peak was during period B.

The increasing rate after load during period C was 17.1% ($P < 0.05$) in the group RH followed by the groups AH (13.0%, not significant) and NN (10.2%, $P < 0.01$). In the normal controls slight increase (5.2%) was only seen in period B but was not significant.

Mean NcAMP (Fig. 5)

The curve in the group PHPT was above 4.0 n mol/100 ml GF and never fell to within the normal range, but the

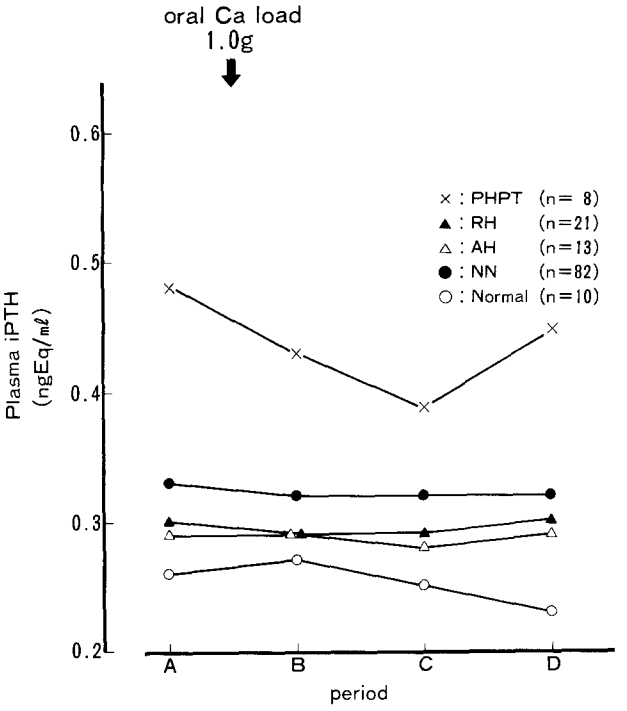

Fig. 6. Changes in mean plasma immunoreactive parathyroid hormone (iPTH) before and during oral calcium tolerance test in the 5 groups. No significant difference is seen at periods B, C and D vs. period A

curves in the remainder were below 3.0 n mol/100 ml GF. Among the latter 4 groups, the curve in the group RH was highest followed by the curves in groups AH, NN and in normal controls.

The curves in groups PHPT, RH, AH and NN showed nadirs in the period B, but a significant difference ($P < 0.001$) only occurred between the values of the periods A and B in the group NN, in which the mean reduction rate was 23.8%. In the normal controls no nadir was observed.

Mean Plasma iPTH (Fig. 6)

The curve in the group PHPT was above 0.39 ngEq/ml, which, though within the normal range, was higher than the levels in the remaining 4 groups.

The nadir was seen in period C in the groups PHPT and AH, but was obscure in the groups NN and RH. In the normal controls, there was no nadir, rather an indistinct peak was evident in period B. No significant differences were seen between the plasma iPTH levels before and during the test in the 5 groups.

Discussion

In the current study, the mean increases of serum Ca (Δ 0.4–0.8 mg/dl) in response to oral Ca load, which are consistent with reports of Broadus et al. [3] and Evans et al. [4], were less remarkable than those (Δ 2.5–3.0 mg/dl) obtained after intravenous Ca infusion [2, 7]. As a result, changes in the other parameters were also less distinct especially in the assessment of parathyroid suppressibility by determination of NcAMP and plasma iPTH, in which nadirs are likely to be at the period B and period C, respectively, but significant decrease was obtained only in NcAMP value of the group NN.

The indistinct suppression obtained by determination of plasma iPTH was due to the antibody used which has affinity only for the carboxy terminal of the PTH molecule. A small change in the level of intact PTH molecules may not be easily detected as a distinct alteration because both a large amount of carboxy terminal fragments, which are not biologically active, and a relatively small amount of intact PTH molecules are mixed in plasma. Moreover, RIA of PTH is not as yet completely established and is not as reliable as NcAMP which reflects parathyroid function more rapidly and more sensitively than plasma iPTH [1]. In fact, the changes in plasma iPTH level during the test are very small and differences may not be meaningful. Therefore, only the changes in NcAMP as a means of assessing parathyroid suppressibility will be discussed hereafter.

In the all 5 groups, though a small number of exceptions exist, there was a tendency for serum Ca to peak and NcAMP to have a nadir in period B, respectively, while urinary Ca/Cr ratio, serum P and $TmPO_4$/GFR peaked in period C, suggesting that intestinal Ca absorption and parathyroid suppression due to the raised serum Ca level occur during the 2 hours after load, and urinary Ca excretion, serum P and $TmPO_4$/GFR increased from 2 to 4 hours after load.

The exceptions to this generalisation was the change of $TmPO_4$/GFR in the group PHPT and also the level of NcAMP in the normal controls. The mean $TmPO_4$/GFR in the group PHPT did not rise but rather fell constantly (though not significantly) during the test, which indicated that the mean urinary P excretion during oral Ca load may not have been influenced by the raised serum Ca level but rather by diurnal rhythm [5]. These results may indicate, as a whole, parathyroid autonomy in the group PHPT. On the other hand, there was no autonomy in the changes of mean $TmPO_4$/GFR in the remaining 4 groups, among which, however, there were large overlaps between levels before and during the test and some cases showed a tendency to decrease during the test. Therefore, it would not be appropriate to use the change in $TmPO_4$/GFR for differenciating PHPT from normals in individual cases.

The change of mean NcAMP in the normal controls was hardly seen, possibly because the serum Ca change (Δ 0.4 mg/dl), which was smallest among the 5 groups, was too small to affect the NcAMP level. The result was not in agreement with reports of Pak et al. [11] and Broadus et al. [3], which demonstrated a significant reduction in spite of similar increases in serum Ca.

The rise in the mean serum P level during the test was small but significant in the groups NN and RH. Similar results, though during Ca infusion, were obtained by us

(data not published) and Howard et al. [6]. This phenomenon may be accounted for by both increased $TmPO_4$/GFR and parathyroid suppression, but the true reason is unknown.

With regard to the parathyroid suppressibility assessed by NcAMP, it was observed that parathyroid activity tended to be suppressed in every group except for the normal controls although the suppression was very slight and was variable between cases. 25% of the PHPT group showed paradoxical increase (detailed data will be published later) during the test, and the mean NcAMP level never fell to within the normal range with almost no exceptions. A similar tendency was observed in the mean plasma iPTH level of the group PHPT. The facts may indicate that in some cases of PHPT patients show parathyroid autonomy and in others abnormal suppressibility occurrs as reported by Broadus et al. [3].

We examined the biochemical changes before and during oral Ca load. The period D was not mandatory for performing the test since all peaks and nadirs appeared during the periods B or C.

In conclusion, oral Ca tolerance test may not be as effective as Ca infusion test for suppressing parathyroid activity. However, it is simple and safe, moreover, is useful not only for differentiation among NN, AH and RH but also for the diagnosis of PHPT by demonstrating parathyroid autonomy or abnormal suppressibility assessed by NcAMP and/or $TmPO_4$/GFR.

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Tadaichi Kitamura, MD
Department of Urology
Branch Hospital
Faculty of Medicine
University of Tokyo
Mejirodai, Tokyo
112 Japan