EFFECTS OF PHOSPHATE LOADING AND DEPLETION ON THE RENAL EXCRETION AND REABSORPTION OF INORGANIC PHOSPHATE

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A number of studies have indicated that parathyroid extract increases the renal excretion of phosphate (1-6). This effect appears to result from a depression of the renal reabsorption of phosphate (6). Endogenous secretory activity of the parathyroid glands has been related to the extracellular concentration and/or the dietary intake of calcium and phosphate. Although dietary variations of these ions did not correlate consistently with TmP³ in our initial investigations (7), other workers have demonstrated an influence of diet on phosphate reabsorption. A high phosphate diet led to a diminished P reabsorption in normal but not in parathyroidectomized rats (8). Studies in dogs (9) and in normal human subjects (8, 10) also indicated that the level of P intake influenced P reabsorption, but whether this effect was mediated by the parathyroid glands is not clear. In order to examine more rigorously the effects of a high P intake, buffered sodium phosphate solutions were administered intravenously daily for four to eight days to the normal and hypoparathyroid subjects previously described (7). Another phase of this study involved an inquiry into the mechanism by which aluminum gels produce a marked reduction in urinary P.

Variations in plasma levels of Ca and P often occur together. An attempt was made to separate the effects of elevation of plasma P from the frequently seen simultaneous reduction in plasma Ca.

Our data indicate that repeated daily intravenous administration of large quantities of phos-

phate results in a reduction in renal P reabsorption. This effect does not appear to depend upon an associated reduction in plasma Ca. Whether this effect is mediated via the parathyroids cannot be conclusively stated. The results indicate that aluminum gels produce their effect primarily, and perhaps solely, by effecting a reduction in plasma P.

METHODS

These studies were conducted on the same patients previously described, and the measurements of TmP were carried out by the method detailed in an earlier paper (7). In studies of the effects of intravenously administered phosphate, a buffered sodium phosphate solution, pH 7.4, was infused over a 4 to 6-hour period on four consecutive days. Five subjects received 75 mM of P each day; two subjects, C. H. and D. F., received 90 and 150 mM P per day, respectively. Two of the normal subjects, C. H. and E. P., received eight daily P infusions, and on the last four days they received, in addition, infusions of Ca. The Ca was administered as calcium gluconate, 15 mg. Ca per kg. of body weight in 1,000 ml. of 5 per cent glucose in water, over a four-hour period starting several hours after the completion of the phosphate infusion. Infusions of di-sodium ethylenediamine tetraacetic acid (EDTA) were given to the four normal subjects who received intravenous phosphate. Four gm. of EDTA was administered in 1,000 ml. of 5 per cent glucose in water over a 4 to 6-hour period daily for four consecutive days. TmP was measured prior to, and on the day following completion of the P or EDTA infusions.

In the studies on the effects of aluminum gels 180 ml. of basic aluminum carbonate (Basaljel®) was administered orally each day in four divided doses, one hour after meals and at bedtime, for 6 to 21 days. Concomitantly, the subjects received a low dietary P intake of 600 to 800 mg. per day. Balance studies carried out during aluminum gel administration were performed on the metabolic ward in the manner described by Deitrick, Whedon, and Shorr (11).

Chemical methods and calculations used in these studies were the same as those described in a previous communication (7).

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³ As in the previous papers, the following abbreviations have been used: Ca, calcium; P, inorganic phosphate; Tm, maximum renal tubular rate of transfer.

TABLE I

Effect of intravenous sodium phosphate on the maximal phosphate reabsorption in a normal male before (A) and after (B) four daily infusions each containing 150 mM P

Total concurrent time <i>min.</i>	Urine flow <i>ml./min.</i>	C_{In} <i>ml./min.</i>	C_{PAH} <i>ml./min.</i>	Plasma P $\mu M/ml.$	Urine P $\mu M/ml.$	Phosphate		
						Filtered $\mu M/min.$	Excreted $\mu M/min.$	Reabsorbed $\mu M/min.$
A. Control								
0	14.5			1.01	1.55		22	
71	Intravenous buffered sodium phosphate delivered at 0.5 mM/min.							
129-159	12.4	119	500	2.76	17.2	328	214	114
159-189	11.2	110	495	3.11	22.2	342	249	93
189-219	10.1	116	517	3.31	28.2	384	285	99
B. After 4 daily phosphate infusions—150 mM/day								
0	15.3			0.59	3.86		59	
45	Phosphate infusion at 0.5 mM/min.							
103-135	9.5	99	516	1.97	21.4	195	203	—8
135-173	9.1	105	509	2.48	28.9	260	264	—4
173-202	10.7	107	525	2.82	27.4	302	293	9

TABLE II

Summary of effects of phosphate infusions on normal and hypoparathyroid subjects

		TmP		Plasma* P μ M/ml.	Plasma* Ca mg. %	Urine* P μ M/min.
		μ M/min.	% control			
Normals						
C. H.	Before P	256	100	1.42	9.2	17
	After P	197	77	1.26		32
	After P and Ca†	168	66	1.08	10.20	25
D. F.	Before P	102	100	1.01	9.9	22
	After P	0	0	0.59	10.1	59
W. R.	Before P	137	100	0.97	10.30	12
	After P	59	43	0.83	9.24	30
E. P.	Before P	110	100	1.09	11.20	9
	After P	70	64	1.06	10.20	24
	After P and Ca†	45	41	0.95	8.86	29
Hypoparathyroid						
A. W.	Before P	149	100	1.37	7.10	10
	After P	134	90	1.50	5.67	3
B. C.	Before P	84	100	0.91	7.6	5
	After P	64	76	0.87	7.6	3
L. D.	Before P	102	100	0.79	8.89	0.8
	After P	40	39	0.74	8.35	5.0

* Specimens obtained before the first daily P infusion and the day following the last P infusion and prior to inulin-phosphate infusions for determination of TmP.

† Four additional daily phosphate infusions were given together with 4 daily infusions of calcium gluconate (15 mg. Ca per kg.) given over a 4 to 6 hour period several hours after the phosphate infusions had been completed.

RESULTS

Effects of intravenous phosphate in normal subjects

The administration of four daily intravenous infusions of P to one normal subject led to a fall in

P reabsorption from an average of 102 μ M per min. to 0 (Table I). A significant reduction in TmP was also noted in three other normal subjects (Table II). It was found that the administration of Ca infusions to subjects receiving P in-

TABLE III
Effect of EDTA infusions on plasma concentrations and urinary excretion of Ca and P

			Plasma Ca mg. %		Plasma P μM/ml.		Urine Ca mg./24 hr.	Urine P mM/24 hr.
			Before	After	Before	After		
Normals								
D. F.	3/3-4	4 gm. di-Na EDTA	9.79	9.15	1.07	0.87	353	
	3/4-5	4 gm. di-Na EDTA	8.79	8.85	0.89	0.69	338	
	3/5-6	4 gm. di-Na EDTA	9.55	8.78	1.01	0.89	370	
	3/6-7	4 gm. di-Na EDTA	10.35	9.40	1.12	0.76	280	
E. P.	4/10-11	Control					62	18.2
	4/11-12	4 gm. di-Na EDTA	11.00	9.60	1.12	0.92	356	20.0
	4/12-13	4 gm. di-Na EDTA	10.90	9.30	1.02	0.86	364	20.1
	4/13-14	4 gm. di-Na EDTA	10.30	9.20	1.11	0.87	298	16.8
	4/14-15	4 gm. di-Na EDTA			1.17	0.72	350	16.3
	Diet: 135 mg. Ca; 570 mg. P daily							
W. R.	11/15-16	4 gm. di-Na EDTA	9.58	8.57			413	46.0
	11/16-17	4 gm. di-Na EDTA	9.03	6.48	0.89	0.77	392	33.0
	11/17-18	2 gm. di-Na EDTA					189	26.0
	11/18-19	4 gm. di-Na EDTA					294	29.0
Diet: 130 mg. Ca; 1,200 mg. P daily								
C. H.	4/14-15	4 gm. di-Na EDTA	8.45	7.55	1.25	1.24		
	4/15-16	4 gm. di-Na EDTA						
	4/16-17	4 gm. di-Na EDTA						
	4/17-18	4 gm. di-Na EDTA						
	4/18-19	4 gm. di-Na EDTA	9.45	8.20	1.29	1.47		

fusions did not reverse the downward trend in TmP (Table II).

A decrease in endogenous plasma P levels as a consequence of P infusions was seen in the normal subjects, but there was no consistent change in plasma Ca (Table II). It was noted that the endogenous urinary excretion of phosphate increased in the face of a decreasing plasma P level, a finding consistent with a reduced tubular P reabsorption.

Effects of phosphate infusions in hypoparathyroid subjects

The results of P infusions in three hypoparathyroid subjects are shown in Table II. In A. W., the most severely hypoparathyroid subject, the re-

duction in TmP was less than that seen in normal individuals. However, the other two hypoparathyroid subjects, whose disease was considerably milder, showed reductions in TmP as great as those seen in the normal subjects. It can be seen that the endogenous plasma P levels and P excretion changed very little in the hypoparathyroid individuals.

Effects of EDTA infusions in normal subjects

Because an elevation of plasma P is usually accompanied by a reduction of plasma Ca one must consider the possibility that the effects observed when the plasma P is high may actually result from a lowered plasma Ca. The administration of di-sodium ethylenediamine tetraacetic acid (EDTA), permitted a reduction in the circulating Ca, particularly the ionized fraction, without a concomitant increase in plasma P. The effects of intravenous EDTA administration are summarized in Table III. The fall in plasma calcium seen following an infusion of EDTA actually represents a reduction in the oxalate-precipitable, and, presumably, in the ionized calcium. The urinary excretion of Ca is considerably elevated by the administration of EDTA. It can also be seen that

TABLE IV
Effect of EDTA on TmP in four normal subjects

Subject	Control TmP μM/min.	After EDTA	
		μM/min.	% Control
C. H.	256	247	97
D. F.	102	118	116
W. R.	137	146	107
E. P.	110	112	102

a drop in plasma P usually occurred following EDTA administration. That this result is not explained by an augmented urinary P excretion is apparent from the excretion data on E. P. No effect of EDTA on TmP was noted in four normal subjects (Table IV).

Administration of aluminum gel

Oral administration of aluminum gel produced a reduction in fasting plasma P levels and in urinary excretion of P in normal individuals and in the one hypoparathyroid subject studied (Table V). There was a profound drop in plasma P in the hypoparathyroid subject, A. W., on two occasions and in one normal individual, E. E. Why the latter reacted in this fashion on only one occasion is not clear; the daily dose of gel and the dietary P level were similar on another occasion when a much less profound fall in plasma P occurred. The fall in plasma P in A. W. as a result of aluminum gel regimen was not altered by the daily administration of as much as 400 units of parathyroid extract. Calcium, phosphorus, and nitrogen balance studies were carried out in the hypoparathyroid subject and in one normal individual before and during a course of aluminum gel. It can be seen (Figure 1 and Figure 2) that the administration of the gel resulted in an essentially P-free urine. A negative P balance was observed in both subjects but was much greater in the hypoparathyroid individual, and could be accounted for by an increased fecal P. Nitrogen balance was not significantly affected by the gel but calcium balance became more markedly negative in the normal subject during the period of gel administration (Table VI). The high calcium intake in the hypoparathyroid patient largely reflects supplements of calcium chloride solution which were required to prevent tetany.

DISCUSSION

Although acute elevations of plasma P rarely alter TmP (7), repeated daily intravenous P infusions result in a reduction in TmP in normal subjects. The decrease in endogenous plasma P together with an increased endogenous P excretion in one subject (D. F.) are suggestive of the findings in hyperparathyroidism. It is of interest that there was no appreciable change in plasma Ca

associated with the marked decrease in plasma P. Hence, if parathyroid activity were increased, one must postulate either a separation between the principle altering tubular reabsorption of P and the factor which influences calcium metabolism, or a greater sensitivity of the renal tubule to the parathyroid hormone. The decrease in P reabsorption with P infusions is in keeping with the experiments on rats and humans fed high P diets (8). From our data it is not possible to be certain that the reduction in TmP was a result of parathyroid stimulation. Although there was little change in the TmP of the most severely hypoparathyroid subject, A. W., after P infusions, two mildly hypoparathyroid patients showed reductions of TmP comparable to those seen in the normal individuals. Although we are inclined to the belief that the reduction in TmP in these latter two subjects resulted from stimulation of existing parathyroid remnants, this conclusion cannot be definitely stated from our data.

TABLE V
Effect of aluminum gel on fasting plasma P and on urinary P excretion

Subject	Dietary P mg./day	Days on aluminum gel	Plasma P μ M/ml.	Urine P μ M/min.
Normals				
C. H.	1,800	None	1.21	9.0
	700	7	1.02	0.3
	3,000	None	1.19	31.0
	600	7	0.91	0.2
D. F.	1,000	None	0.89	7.8
	600	10	0.62	0
J. N.	Ad lib.	None	1.31	8.0
	600	14	1.11	1.0
E. E.	1,800	None	1.02	9.0
	600	11	0.86	0.1
	1,200	None	1.11	14.0
	600	6	0.42	0
R. H.	3,000	None	1.13	39.0
	600	None	1.05	3.0
	600	10	0.80	0
Hypo-parathyroid				
A. W.	Ad lib.	None	1.51	2.7
	600	10	0.23	0
	725	None	1.49	3.2
	725	15	0.16	0

FIG. 1. THE EFFECTS OF ALUMINUM CARBONATE GEL IN A NORMAL SUBJECT UPON PLASMA P AND P BALANCE

The reduction in TmP seen with phosphate infusion does not appear to be the result of the slight fall in serum calcium which occurred in most of these studies. The binding of a portion of the extracellular calcium by intravenously administered di-sodium EDTA resulted in an increase in the urinary excretion of calcium together with a reduction in the oxalate-precipitable plasma calcium. Although the decrease in plasma calcium was comparable to that seen during phosphate infusions, no reduction in TmP was noted after four daily EDTA infusions. Thus, it appears that the reduction in TmP seen with repeated administration of intravenous phosphate solutions results from a direct effect of the phosphate ion rather than from an associated decrease in the ionizable calcium. Furthermore, when calcium gluconate was infused into those patients receiving phosphate, there was no reversal of the phosphate depression of TmP. The infusion of calcium alone has been shown to reduce phosphate excretion as a result of increased tubular phosphate reabsorption (12). This effect is probably due to inhibition of parathyroid secretion (12, 13). Hence, our data indicate that the effect of phosphate administration on tubular phosphate reabsorption is

FIG. 2. THE EFFECTS OF ALUMINUM CARBONATE GEL ALONE AND IN COMBINATION WITH PARATHYROID EXTRACT IN A HYPOPARATHYROID SUBJECT UPON PLASMA P AND P BALANCE

not altered by any parathyroid-inhibiting influence exerted by calcium.

The oral administration of aluminum gels is regularly followed by a reduction in urinary P (10, 14, 15). In normal and hypoparathyroid subjects the administration of the gel resulted in a decrease in plasma P as well as in urinary P, but there was no consistent effect on TmP. Thus, it appears that the decrease in urinary P which follows administration of aluminum gels is explained by a reduction in the filtered load of P delivered to the renal tubules. In the face of an unchanged tubular P reabsorption a fall in filtered P leads to a decrease in P excretion. Conceivably, it is possible to demonstrate in the normal individual a fall in TmP (*e.g.*, with repeated phosphate infusions), but not a rise, because reabsorption of P by the renal tubules under normal conditions approximates their maximal capacity, and hence what approaches a "hypoparathyroid" state. This was demonstrated in a severely hypoparathyroid subject who had determinations of TmP in the untreated state and when he was receiving adequate parathyroid extract to render him "isoparathyroid." The TmP in the second situation was only slightly less than when the patient was un-

TABLE VI

Effect of aluminum carbonate gel on calcium, phosphorus, and nitrogen balance in normal and hypoparathyroid subjects

Subject	Period*	Calcium (gm./day)				Phosphorus (gm./day)				Nitrogen (gm./day)			
		Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance
R. H. Normal	I	0.130	0.102	0.166	-0.138	0.610	0.349	0.207	+0.054	8.56	7.72	1.00	-0.16
	II	0.130	0.072	0.246	-0.188	0.610	0.437	0.372	-0.199	8.56	8.21	1.27	-0.92
	III†	0.130	0.139	0.291	-0.300	0.610	0.030	0.710	-0.130	8.56	6.75	1.10	+0.71
	IV†	0.130	0.226	0.320	-0.416	0.610	0.000	0.757	-0.147	8.56	7.22	1.32	+0.02
A. W. Hypo- para- thyroid	I	3.406	0.286	2.983	+0.137	0.725	0.142	0.399	+0.184	9.10	8.99	0.76	-0.65
	II	3.406	0.213	2.452	+0.741	0.725	0.022	0.349	+0.354	9.10	7.28	0.91	+0.91
	IV†	3.406	0.158	3.011	+0.237	0.725	0.003	1.160	-0.438	9.10	6.43	1.64	+1.03
	V†	3.406	0.241	2.753	+0.412	0.725	0.000	0.901	-0.176	9.10	7.28	1.21	+0.61

* Each period 5 days in length.

† Aluminum carbonate gel 180 ml./day.

treated (6). If this is the case, then a slight rise in TmP might occur following the administration of aluminum gel and yet not be detectable in studies of this type.

Very striking negative phosphorus balances were produced by the administration of aluminum gel to normal and hypoparathyroid subjects. The much larger negative balance seen in the hypoparathyroid subject was accompanied by a much more profound drop in his plasma P. Whether this greater fecal loss of P and greater drop in plasma P can be ascribed to the hypoparathyroidism cannot be stated. It was postulated that the profound fall in plasma P in the hypoparathyroid patient on aluminum gel may have reflected an inability to mobilize skeletal stores of P. The inadequacy of this hypothesis, however, was demonstrated by the absence of change in the plasma P level upon the administration of as much as 400 units of parathyroid extract daily.

The fall in plasma P which usually followed the administration of EDTA is to be compared with the rise observed in patients who are given calcium infusions (13). This decrease in plasma P was clearly not the result of any alteration in P excretion but is consistent with the postulate that the level of plasma Ca influences the distribution of phosphate (16).

CONCLUSIONS

1. Repeated administration of intravenous buffered phosphate solutions to normal males and females resulted in pronounced reduction in TmP.
2. In one severely hypoparathyroid subject

phosphate infusions produced a minimal drop in TmP while in two subjects with less marked hypoparathyroidism a reduction in TmP comparable to that seen in normal individuals occurred. Although it seems likely that the effect on tubular reabsorption is exerted through the parathyroids, our data are inadequate to establish this relationship.

3. The reduction in TmP appeared to be correlated with an increase in plasma P rather than from any associated reduction in plasma calcium.

4. The reduction in urinary excretion of phosphate following aluminum gel administration appears to be due primarily to a reduction in endogenous plasma phosphate levels.

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