Change in Plasma Phosphate Concentration on Infusion of Calcium Gluconate or Na_2EDTA (34754)

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In 1929, Albright and Ellsworth (1) proposed that a reciprocal relationship existed between the concentration of plasma calcium and plasma phosphate. Although this proposal has withstood the test of time under most circumstances, one of the few exceptions to this rule has been the response of plasma phosphate to the infusion of calcium or disodium ethylenediaminetetraacetate (Na_2EDTA). Several investigators have observed a rise in plasma phosphate associated with the infusion of calcium in euparathyroid man (2, 3) and dog (4) and a fall in plasma phosphate with the infusion of Na_2EDTA in normal man (5, 6). It was suggested that these responses in plasma phosphate were the result of an alteration of plasma calcium effecting the release of parathyroid hormone by the parathyroid glands. The fact that a rise in plasma phosphate on the infusion of calcium in hypoparathyroid patients was observed by one investigator (7) cast some doubt on the role of the parathyroids in primarily mediating this response. In the present study normal and thyroparathyroidectomized dogs were infused intravenously at a constant rate with different concentrations of calcium gluconate or Na_2EDTA until steady-state concentrations of calcium were achieved. We wanted to: (a) define the role of the thyroid–parathyroid system on the response of plasma phosphate to alterations in plasma calcium, (b) describe quantitatively the relationship between the rate of infusion of calcium or Na_2EDTA and the magnitude and duration of the alterations in plasma phosphate that resulted.

Methods. Trained, unanesthetized, catheterized, female mongrel dogs weighing between 10 and 20 kg were used. Infusion solutions consisted of 0.15 *M* sodium chloride plus either calcium gluconate or Na_2EDTA. The volume of solution infused intravenously was always 5 ml/kg/hr. The solution was infused for 12 hr by a constant infusion pump into an indwelling catheter. Calcium gluconate was infused at rates which ranged from 2 to 7 mg of Ca/kg/hr. The infusion solution for 0 mg of Ca/kg/hr was simply isotonic saline. Since the dissociation of CaEDTA is negligible, the rates of Na_2EDTA infusion were expressed in terms of negative stoichiometric equivalents of calcium. They ranged from -2 to -4 mg of Ca/kg/hr. The diet of the thyroparathyroidectomized dogs was supplemented daily with 10 g of calcium lactate and 30 mg of thyroid powder. The details of the mechanics of infusion, collection of blood for analyses and methods of chemical analyses is described by Hausmann and Riggs (8).

Results. The results are summarized in Figs. 1 and 2. In normal dogs there was a direct relationship between the magnitude of the change in plasma phosphate concentration and the concentration of either calcium gluconate or Na_2EDTA infused. The maximum change in plasma phosphate concentration was reached by the eighth hour of infusion. The average plasma calcium preinfusion concentration of the normal dogs was 10.37 ± 0.12 mg/100 ml. In thyroparathyroidectomized dogs there is a direct relationship between the change in plasma phosphate concentration of a similar order of magnitude and the concentration of calcium gluconate infused. One discrepancy in this direct rela-

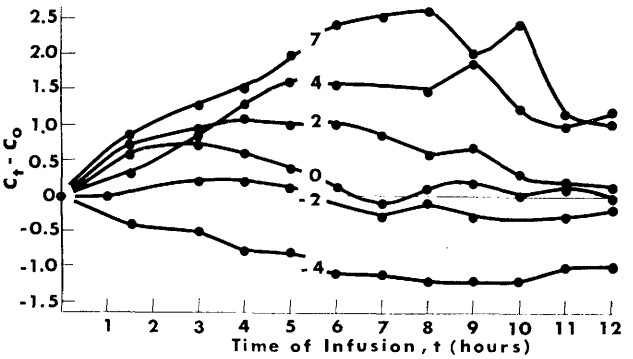

FIG. 1. The effect of the infusion of calcium gluconate or Na_2EDTA at a constant rate on the change in plasma phosphate concentration as a function of the length of time of infusion in normal dogs. C_t is the phosphate concentration in plasma (mg/%) at time t, C_o is the initial preinfusion concentration. Each point represents the average change in plasma phosphate at a particular time t, of all normal dogs infused with the same concentration of calcium or Na_2EDTA. The numbers associated with the curves identify the rate of infusion used (mg of Ca/kg/hr). The points making up each curve represent an average of a minimum of four experiments.

tionship was observed in that a greater change in phosphate concentration was elicited by an infusion of 5 than 7 mg of Ca/kg/hr. The maximum change in plasma phosphate concentration is reached by the sixth hour of infusion. The average plasma calcium preinfusion concentration of the thyroparathyroidectomized dogs was 5.75 $\pm$ 0.58 mg/ml.

Discussion. An elevation in the plasma calcium concentration results in two well-documented endocrine responses: (i) the output of parathyroid hormone into the circulation by the parathyroid glands is reduced (9); (ii) the output of thyrocalcitonin into the circulation by the thyroid glands is enhanced (10). The former, by itself, results in an elevation of plasma phosphate (11); whereas the latter, by itself, results in a decrease in plasma phosphate (12). If the alteration in the plasma phosphate on calcium infusion in the normal animal were solely the result of changes in parathyroid hormone and thyrocalcitonin concentration in the cir-

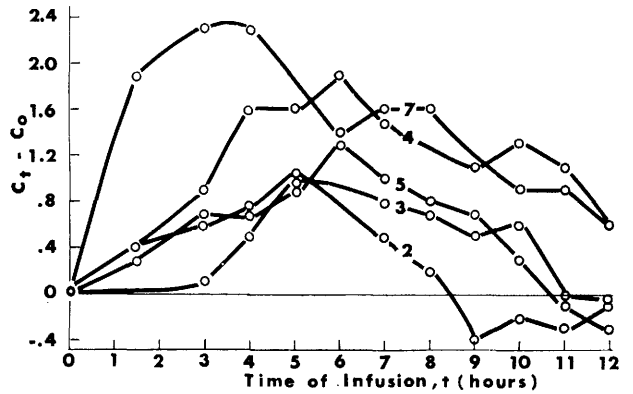

FIG. 1. The effect of the infusion of calcium gluconate or Na_2EDTA as a constant rate on the change in plasma phosphate concentration as a function of the length of time of infusion in thyroparathyroidectomized dogs. The points making up the curves for the infusion of 7, 5, and 3 mg of Ca/kg/hr represent an average of three experiments and the remaining curves an average of two experiments.

culation, the following changes in plasma phosphate concentration would be theoretically possible: (i) an elevation; (ii) a depression; and (iii) no change. The actual change in plasma phosphate would depend on the relative magnitude of the alteration in the activity of the parathyroid and thyroid glands. The fact that we observe an elevation in plasma phosphate suggests that the alteration in parathyroid activity is of greater functional significance, if one assumes that the change in plasma phosphate concentration on calcium or EDTA infusion in the normal animal is *solely* the result of alterations in the activity of the thyroid and parathyroid glands. Since the changes observed in plasma phosphate concentrations in thyroparathyroidectomized animals are very similar to those seen in normal animals, it suggests that the above assumption is incorrect. Our results, therefore, lead to the conclusion that the changes in plasma phosphate concentration on infusion of calcium or EDTA into normal animals are independent of *both* thyroid and parathyroid glands together.

The response to calcium infusion of normal and thyroparathyroidectomized animals was similar when one compared animals infused at the same rate. This result is intriguing in the light of the marked differences in the preinfusion concentration of plasma calcium in the two groups of dogs. The effect therefore seems more dependent on the rate of calcium infusion than on the plasma calcium concentration itself. Some influence of the parathyroids and/or thyroid, however, was apparent as indicated by the earlier appearance of the maximum response in plasma phosphate concentration in the thyroparathyroidectomized animals. Other investigators, who have studied the change in plasma phosphate in response to a calcium load, indicate that the effect could not have been mediated via a change in the kidney excretion of phosphate (3, 4). They suggest that the change in plasma phosphate is a result of a shift of phosphate from the intracellular to the extracellular compartment. Collection of urine by an indwelling catheter indicated that our dogs were in positive water balance during the first 5 to 8 hr of infusion. Therefore, the alterations in plasma phosphate observed were dampened by this dilution effect. The mechanism of the phosphate shift is presently not yet understood.

Summary. The change in plasma phosphate concentration was studied in unanesthetized dogs by continuously infusing calcium gluconate or Na_2EDTA intravenously at a constant rate until the plasma calcium obtained a steady state. The changes in plasma phosphate concentration in the normal and thyroparathyroidectomized animals were primarily dependent on the rate of calcium infusion and independent of both thyroid and parathyroid glands together.

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