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Influence of an Orally Administered Calcium-Binding Cation Exchanger on Calcium Metabolism in the Rat

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Summary. The kinetics of calcium metabolism in the rat were analysed by doing a calcium balance and an assay with ^{45}Ca after feeding a calcium-binding ion exchanger during 3 weeks. Serum and urine concentrations of inorganic phosphate and of calcium were estimated. The increase in the size of the exchangeable calcium pool, the activation of bone turnover, the hypophosphataemia and hyperphosphaturia, as well as hypercalciuria are evidence for a reactive hyperparathyroidism. The results of these experiments call for further investigations concerning the influence of cation exchangers on bone metabolism under clinical conditions.

Key words: Calcium-binding cation-exchanger, calcium metabolism, rat.

INTRODUCTION

Orally administered ion exchangers are being increasingly recommended for the prevention of recurrent calcium stones (6, 10). The aim is to reduce intestinal calcium absorption in order to lower calcium excretion and saturation of calcium oxalate in the urine.

However, stimulation of the parathyroids by a long-standing artificial reduction of intestinal calcium absorption may occur (5).

The present experiments which analyse the kinetics of calcium in the rat were intended to show possible side effects of long-standing treatment with an ion exchanger.

MATERIAL AND METHODS

22 experimental animals (female Wistar rats, starting weight 135-150 g) received 30 g/kg of diet of a cation exchanger (Campanyl, Temmler Werke, Marburg, FRG) mixed into the food during 3 weeks (ground diet, Nafag Nr. 900, Nafag Gossau, SG, Switzerland). 21 control animals were pair-fed with the experimental animals and on the same diet without the ion exchanger. This feeding period was followed by a 3 day metabolism trial consisting of a calcium balance and an analysis of calcium kinetics. At the same time, inorganic phosphate concentrations in the serum and the urine were estimated. The animals were kept in special metabolism cages which allowed a very precise determination of calcium intake with food and of its excretion with urine and faeces. The analysis of calcium kinetics is done by applying the model of calcium metabolism conceived by Aubert and Milhaud (1). The data are obtained through the observation of the decreasing curve of specific radioactivity in the blood serum after intravenous injection of a tracer dose of ^{45}Ca, and of measuring the radioactivity excreted in urine and faeces. The curve is established by plotting time against the measured activities in 0,1 ml of blood taken from the retro-orbital sinus at 2, 4, 6, 24, 32 and 48 hours after injection of the tracer. After 72 hours, the animals were killed and serum taken for analysis of calcium and inorganic phosphate (SMAC = High-speed computer-controlled biochemical analyser, Technicon Instruments Corp., Tarrytown).

The model (Fig. 1) consists of 2 compartments P and E. P includes the calcium of the blood, of the extracellular fluids, the greater part of the

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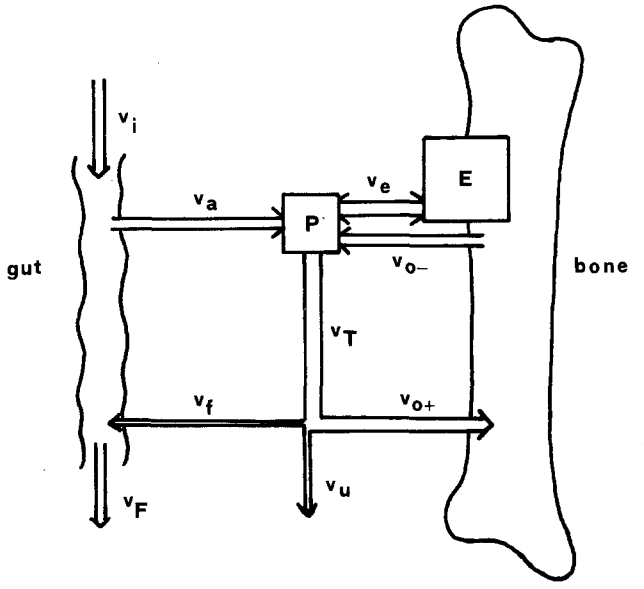

Fig. 1. Model of Ca-metabolism (see explanations in text)

Table 1. Median values and standard deviations of the highly significantly (+++ = P <0,0001) changed parameters of the experimental (EA) and the control animals (CA)

Parameter	EA (n = 22)		CA (n = 21)	
P mg	37.90	±2.31 +++	15.82	±1.54
v_e mg/d	125.12	6.54 +++	64.63	2.52
v_T mg/d	102.71	4.49 +++	44.84	1.55
v_{ux} mg/d	0.87	0.05 +++	0.61	0.05
v_{o+} mg/d	97.31	4.29 +++	39.81	1.58
v_{o-} mg/d	80.12	4.56 +++	24.95	1.97
iP (serum, mg%)	6.98	0.80 +++	8.50	0.96
iP (urine, mg)	54.91	8.31 +++	33.67	5.03

calcium of the soft parts, and a fast exchanging fraction of bone calcium. Compartment E comprises mainly a slowly exchanging fraction of bone calcium.

There is a reversible exchange (v_e) between P and E. P receives calcium from the intestine (v_a) and from the bone (v_{o-}); it loses calcium irreversibly (v_T) via bone accretion (v_{o+}), and the excretion with the urine (v_u) and the digestive juices (v_f). The values for the parameters of the model may then be calculated from the experimental data.

RESULTS

In Table 1, the values for the parameters of calcium metabolism which show statistically highly significant (p <0,001) alterations in the experimental animals (EA) are listed and compared with those of the control animals (CA). In the EA, the mass of exchangeable calcium (compartments P and E) is increased by one half. Bone turnover is greatly increased as well, calcium uptake (v_{o+}) and calcium release (v_{o-}) both showing a threefold increase. The calcium balance in both groups was positive. The ratio of intestinal calcium absorption in the EA (va/vi) did not differ from that of the CA. In the EA, serum calcium (S) showed a slight tendency to higher values. Calcium excretion in the urine (v_{ux}) was significantly increased in the EA. Inorganic phosphate showed a highly significant decrease in the serum of the EA, together with a highly significant increase in urinary excretion.

DISCUSSION

Feeding of the cation exchanger during 3 weeks provoked an increase of the size of the exchangeable calcium pool and at the same time an increase in bone calcium turnover. According to the literature (2, 3, 7) this combination indicates an increased secretion of parathormone (PTH) and may even be regarded as typical hyperparthyroidism. The conception prevailing for a long time that PTH stimulates the resorption, but not the formation of bone, is now clearly refuted (7, 8). In several experimental studies (4) and recently also in patients with osteoporosis, an anabolic effect of physiologic quantities of PTH has been shown.

PTH leads to an activation of bone turnover on one hand, and enhances the positive calcium balance on the other, provided that sufficient calcium is present in the food. This does not rule out the efficacy of the cation exchanger, for with the dose given, only about one third of the calcium in the food is bound. After feeding the ion exchanger for 3 weeks there were no differences between the EA and the CA concerning calcium absorption ratio and absolute calcium absorption from the intestine. We propose that a hypoabsorption of calcium with concomitant hypocalcaemia occurs at first and results in a reactive increase in PTH secretion. Thus, calcium absorption from the intestine is normalized, as well as the serum calcium level; on the other hand an activation of bone turnover is induced. The increase in the mass of exchangeable calcium and in bone turnover, the hypophosphataemia and hyperphosphaturia, as well as hypercalciuria together with the elevated serum calcium present good evidence for a reactive hyperparathyroidism induced by the longstanding application of a cation exchanger.

Further evidence is produced by the estimation of cAMP in the urine. The difference in cal-

cium metabolism of the rat with its continuously growing skeleton on one hand, and that of adult man on the other, do not allow direct extrapolation from our experiments to clinical conditions. We may conclude, however, that clinical use of cation exchangers in urinary stone prophylaxis calls for further investigations concerning the influence of these substances on bone metabolism.

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