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Bone extraction and blood clearance of diphosphonate in the dog

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Abstract

The transcapillary extraction of diphosphonate, as [^{99m}Tc]EHDP, a substance used in bone scanning and for management of certain metabolic bone diseases, has been examined. The maximum instantaneous extraction for [^{99m}Tc]EHDP was 0.27 ± 0.05 (mean $\pm$ SD, $N = 10$) and the net extraction at 5 min was 0.18 ± 0.05 ($N = 10$). The permeability ratio of [^{99m}Tc]EHDP to the freely diffusible compound, sucrose, using the formula $PS = -F_s \log_e (1 - E_{\max})$, was 0.71. This is similar to the ratio of diffusion coefficients of EHDP to sucrose, which is estimated to be 0.78. These results suggest that the mechanism by which [^{99m}Tc]EHDP passes through the capillaries in bone is passive diffusion. Tissue level estimations of EHDP confirm a rapid blood clearance associated with an increase in the rate of urinary excretion; the level of [^{99m}Tc]EHDP in bone, however, remains constant. The fractional excretion of [^{99m}Tc]EHDP was $27.3 \pm 2.0\%$ in control dogs and was unchanged by thyroparathyroidectomy and subsequent infusion of parathyroid hormone.

Keywords

EHDP; capillary extraction; diffusion; bone capillary permeability; indicator-dilution technique; renal clearance; parathyroid hormone; bone scanning; technetium-labeled phosphate compounds; tracer exchange; tissue uptake; blood flow

Bone scanning with radioactive isotopes is used with increasing frequency in clinical practice, particularly to detect metastases in bone before they are visible on radiographs (15), to diagnose infections involving bone or joints (2), and to study rates of union of fractures (33).

Until recently, the isotopes available for bone scanning included strontium-85 and -87m, and fluorine-18. However, in 1971, Subramanian et al. (31) labeled a polyphosphate with technetium-99m and introduced the phosphate compounds as bone scanning agents. Of the phosphate compounds currently available, technetium-labeled ethane-1-hydroxy-1,1-diphosphonate ([^{99m}Tc]EHDP) appears to be the best (16).

EHDP is synthesized from acetic acid and phosphorus trichloride and is injected, labeled with technetium, as a stannous salt. It is stable in vivo and binds by chemisorption onto the

hydroxy apatite crystal (18). In therapeutic doses, it inhibits crystal growth, and in patients with osteoporosis large doses of EHDP lead to osteoid formation and to vitamin D-deficiency rickets (17). Currently, EHDP is being used in the treatment of Paget's disease of bone (27). To reach the hydroxyapatite crystal, [^{99m}Tc]EHDP is transported through the capillaries that lie within the Haversian system of the cortex of bone. We have examined the exchange of [^{99m}Tc]EHDP across the capillaries in bone, using the indicator-dilution technique. We have also investigated the uptake by the tissues of [^{99m}Tc]EHDP, its excretion by the kidneys, and the effect of parathyroid hormone on its renal clearance.

Materials and Methods

Extraction and permeability

Ten adult male dogs were anesthetized and the nutrient artery of the tibia was approached by the transfibular route. The nutrient artery was cannulated with fine polyethylene tubing (diameter 0.58 mm). Previous studies have shown that such a cannulation does not decrease total tibial strontium clearance but does decrease diaphyseal clearance by one-third (9). The ipsilateral femoral vein was identified in the femoral triangle and cannulated with polyethylene tubing (diameter 5.3 mm). Tributaries of the femoral vein proximal to the cannula were ligated, and a pneumatic cuff was applied to the thigh and inflated to 60 Torr to prevent recirculation (4). A 1-ml mixture of 30 μCi [^{51}Cr]albumin (Squibb), 10 μCi [^{14}C]sucrose (New England Nuclear), and 20 μCi [^{99m}Tc]EHDP (Diagnostic Laboratories) was injected into the nutrient artery over 1 min so as not to alter total bone blood flow. Twenty sequential samples of venous blood were collected at 15-s intervals from the ipsilateral femoral vein for 5 min. These samples were the total outflow of the femoral vein during that period.

After centrifugation, 1-ml samples of plasma were counted for 2 min in a Nuclear-Chicago instrument, model C120-1, along with a standard. These specimens were recounted at 48 h, with allowance for the decay of technetium. Aliquots of 0.2 ml of the original plasma in 10 ml of Insta-Gel (Packard) were then counted with a Nuclear-Chicago Mark II liquid scintillation system in conjunction with an IBM punch card system and a Control Data 3500 computer.

In four dogs the instantaneous extraction of [^{99m}Tc]pyrophosphate, a compound also used in bone scanning, was determined; and in three dogs the instantaneous extraction and permeability ratio of [^{99m}Tc]EHDP was compared with that of ^{85}Sr .

Calculations of extractions and permeabilities

The observed concentration-versus-time curves of each tracer in the outflow were normalized by dividing by the dose of each tracer injected, to provide three functions, $h(t)$, the fraction of the injected dose appearing in the outflow per second

$$h(t) = \frac{F}{I} \cdot C(t)$$

where F is the flow in the femoral vein, I is the injected dose, and $C(t)$ is the concentration of the tracer in the blood. Because of prolongation of the injection, $h(t)$ does not have the same shape as the curve of probability density function of transit times from inflow to outflow but it has the same dimensions. If the concentration of the reference tracer in the femoral vein at 5 min is zero, then it can be assumed that all the albumin is out of the bone and that the area under the reference tracer is unity. However, the reference may not reach zero in 5 min. For this reason the formula

$$h(t) = \frac{F \cdot C(t) / I}{\int_0^5 h_R(t) dt} \quad (1)$$

is appropriate for the first few minutes after injection when h_R is significantly greater than zero.

The instantaneous extraction for [^{99m}Tc]EHDP, [^{99m}Tc]pyrophosphate, ^{85}Sr , and [^{14}C]sucrose was calculated from the formula

$$E(t) = \frac{h_R(t) - h(t)}{h_R(t)} \quad (2)$$

where $E(t)$ = instantaneous fractional extraction (dimensionless); $h_R(t)$ = fraction of injectate of reference tracer (^{51}Cr]albumin) per second; and $h(t)$ = fraction of injectate of the test tracer ([^{99m}Tc]EHDP, [^{14}C]sucrose, [^{99m}Tc]pyrophosphate, or ^{85}Sr) per second. $E_{\max}$ is the maximum value of the instantaneous extraction and is the peak instantaneous extraction curve. It was taken to be the best indication of extraction before back diffusion becomes appreciable (1).

The permeability of the substance was calculated from the formula developed by Renkin (25) and by Crone (12)

$$PS = -F_s \log_e (1 - E_{\max}) \quad (3)$$

where F_s = flow of the solute-carrying fluid, which in this case is plasma, $\text{ml} \cdot \text{g}^{-1} \cdot \text{min}^{-1}$; P = capillary permeability, $\text{cm} \cdot \text{s}^{-1}$; and S = capillary surface area, $\text{cm}^2 \cdot \text{g}^{-1}$. The ratio of permeabilities of any two permanent tracers can be determined independently of S and F_s , which cancel on the basis that F_s and the surface area of the exchange region are the same for both, as presented by Crone (11)

$$\frac{P \text{ [}^{99m}\text{Tc] EHDP}}{P \text{ [}^{14}\text{C] sucrose}} = \frac{\log_e (1 - E_{\max} \text{ [}^{99m}\text{Tc] EHDP})}{\log_e (1 - E_{\max} \text{ [}^{14}\text{C] sucrose})} \quad (4)$$

The advantage of this equation is that it contains only the values determined in the experiment, whereas a calculation of the permeability coefficient involves assumptions about capillary surface area and rate of perfusion.

For sucrose, molecular weight = 342, the diffusion coefficient, D_{sucrose} , is given by Longworth (21) as $5.2 \times 10^{-6} \text{ cm}^2/\text{s}$ at 20°C or, if corrected, $5.4 \times 10^{-6} \text{ cm}^2/\text{s}$ at 37°C . The molecular weight of $[^{99\text{m}}\text{Tc}]\text{EHDP}$ is 498; a diffusion coefficient for EHDP was calculated by interpolation on Fig. 3.2 of Stein (29), giving a value of $4.0 \times 10^{-6} \text{ cm}^2/\text{s}$ at 20°C or, if corrected, $4.2 \times 10^{-6} \text{ cm}^2/\text{s}$ at 37°C . The ratio of $D_{\text{EHDP}}/D_{\text{sucrose}}$ is 0.78, which can be compared with ratios of their permeabilities. $[^{99\text{m}}\text{Tc}]\text{pyrophosphate}$ does not have a precisely determined molecular weight, but it may be smaller than $[^{99\text{m}}\text{Tc}]\text{EHDP}$.

The net extraction, E_{net} , at 5 min, which is the apparent fractional retention by the bone at that time, is

$$E_{\text{net}} = \frac{\int_0^5 [h_R(t) - h(t)] dt}{\int_0^5 h_R(t) dt} \quad (5)$$

Tibial residue content

At the end of 5 min the dog was killed and the tibia was disarticulated and cleaned of soft tissue. Then the whole bone was counted for $[^{99\text{m}}\text{Tc}]\text{EHDP}$ in a small whole-animal counting chamber to give the fractional residue, $R(t)$, at 5 min

$$R(5 \text{ min}) = \frac{[^{99\text{m}}\text{Tc}] \text{ EHDP in bone at } 5 \text{ min (cpm)}}{\text{dose of } [^{99\text{m}}\text{Tc}] \text{ EHDP (cpm)}} \quad (6)$$

The fractional recovery of the initial $[^{99\text{m}}\text{Tc}]\text{EHDP}$ was obtained by summing the amount retained in the tibia and the amount collected in the femoral vein over the 5-min period

$$\text{recovery} = \int_0^5 h(t) dt + R(5 \text{ min}) \quad (7)$$

Tissue uptake and blood clearance

Eleven male adult dogs were anesthetized and the left jugular vein and right carotid artery were cannulated; a urinary catheter was inserted into the bladder for urine collection.

Thirty microcuries of $[^{99\text{m}}\text{Tc}]\text{EHDP}$ were injected into the jugular vein, and blood samples were withdrawn from the carotid artery at 1-min intervals for 10 min and then at 10-min intervals for between 1 and 4 h. Two animals were killed at 1, 2, and 3 h and five at 4 h, and samples of tissue were taken from the skin, muscle, liver, kidney, lung, gut, and the whole of the left tibia excluding the marrow.

These samples were weighed and counted along with a pilot in the small whole-animal counter. The blood and urine samples were centrifuged, and 1-ml aliquots of plasma and urine were counted along with a pilot for 2 min in a Nuclear-Chicago instrument, model C120-1.

The observed tracer concentrations in tissue and plasma were normalized with respect to the injected dose to give the normalized concentrations, C_t in tissue and C_p in plasma

$$C_t \text{ or } C_p = \frac{\text{cpm/g of tissue or plasma}}{\text{cpm of injected dose}} \quad (8)$$

Fractional uptake, f , by whole tissue is obtained by multiplying by the tissue weight, W_t

$$f = C_t \times W_t \quad (9)$$

The tissue concentration of each time, t , relative to that in the plasma at the same time is C_t/C_p .

Renal clearance

The clearance of [^{99m}Tc]EHDP was measured in four control, unoperated adult male dogs and compared with the clearance of inulin labeled with ^{14}C . The dogs were anesthetized, and the left jugular vein and right carotid artery were cannulated. The bladder was catheterized for urine collection.

Thirty microcuries of [^{99m}Tc]EHDP and 10 μCi of [^{14}C]inulin were injected into the jugular vein, and 1-ml blood samples were withdrawn from the carotid artery at 10-min intervals for 4 h. The bladder was washed out with saline at 10-min intervals and the volume was measured. The samples were centrifuged and 1-ml aliquots of serum and urine were counted for technetium along with a pilot in the Nuclear-Chicago model C120-1. Then 0.2-ml samples of ^{14}C were counted in an automatic liquid scintillation system (Nuclear-Chicago Mark II). Clearance (ml/min) was calculated as

$$C_u \cdot F_u / C_p \quad (10)$$

where C_u is concentration of tracer in urine (cpm/ml), F_u is flow of urine (ml/min), and C_p is concentration of tracer in plasma (cpm/ml), taken as the interpolated average over the period appropriate to each urine collection period, thereby correcting for urinary transit delays.

Parathyroid hormone control

The objective of the renal study was to evaluate the responsiveness of EHDP to parathyroid hormone. These studies were conducted in seven dogs. In three dogs, 4 days after a total thyroparathyroidectomy, the clearance of [^{14}C]inulin was compared with that of [^{99m}Tc]EHDP with the method just described.

In another three dogs, the response of phosphate to parathyroid hormone was compared with [^{99m}Tc]EHDP and [^{14}C]inulin. In these animals after total thyroparathyroidectomy, the ureters were isolated and cannulated. Two hours later an infusion of [^{99m}Tc]EHDP and [^{14}C]inulin was started. Samples of blood and urine were obtained at 15-min intervals for phosphate as well as for [^{99m}Tc]EHDP and [^{14}C]inulin, and steady-state values were used for data analysis. One hour later a pharmacologic priming dose (3.3 units/kg) of parathyroid hormone (Lilly) was given intravenously followed by a sustained dose of 0.1 unit/kg per min. The parathyroid hormone was infused for 1 h in one dog and 2 h in the two others, and

steady-state values were used for data analysis. These isotopes were counted in a similar manner as before and the concentration of phosphate was estimated by a colorimetric method (34).

Results

Extraction and permeability

Figure 1 (upper) shows an example of a typical outflow indicator-dilution curve for the three tracers, calculated from Eq. 1. The EHDP curve is separate from the sucrose curve; however, at about 2 min the sucrose curve crosses the albumin curve, whereas the EHDP curve does not. The extractions for sucrose and EHDP calculated from Eq. 2 are shown in Fig. 1 (lower); the peak is the maximum instantaneous extraction, $E_{\max}$, and the extractions at 5 min are the net extractions. The maximum instantaneous extraction of sucrose ($E_{\max}$) is 0.36 ± 0.08 (mean $\pm$ SD) ($N = 10$) compared with $E_{\max}$ for EHDP which is 0.27 ± 0.05 ($N = 10$). The mean E_{net} calculated from Eq. 5 for sucrose is 0.14 ± 0.09 ($N = 10$) and for EHDP, 0.18 ± 0.05 ($N = 10$). The permeability ratios calculated from Eq. 4 are given in Table 1. The mean $\pm$ SD was 0.71 ± 0.16 .

In the four experiments wherein [$^{99\text{m}}\text{Tc}$]EHDP was compared with [$^{99\text{m}}\text{Tc}$]pyrophosphate, the $E_{\max}$ for pyrophosphate was 0.43 ± 0.08 ($N = 4$) and the E_{net} was 0.36 ± 0.1 ($N = 4$). There was no statistical difference between pyrophosphate and EHDP extraction.

In the three dogs in which strontium was compared with EHDP, there is an obvious difference in extraction between ^{85}Sr and EHDP, as is seen in an example of the outflow dilution curve comparing ^{85}Sr and [$^{99\text{m}}\text{Tc}$]EHDP (Fig. 2, upper). The mean $E_{\max}$ for EHDP was 0.33 ± 0.16 ($N = 3$) and the mean $E_{\max}$ for strontium was 0.75 ± 0.09 ($N = 3$), an example of which is shown in Fig. 2 (lower). Table 2 shows a comparison of extractions.

The amount of [$^{99\text{m}}\text{Tc}$]EHDP remaining in the bone at 5 min, $R(5 \text{ min})$, was 21%. The fractional residue of [$^{99\text{m}}\text{Tc}$]EHDP derived from Eq. 6 at 5 min was 0.215, and the fractional recovery of [$^{99\text{m}}\text{Tc}$]EHDP, Eq. 7, was 99%.

Blood disappearance and tissue uptake

There is a rapid blood clearance of [$^{99\text{m}}\text{Tc}$]EHDP, particularly within the first 20 min, when 80% of the injected dose disappears from the blood. By 4 h, 97% of the original injected dose is removed from the blood. In Fig. 3 the concentration of EHDP expressed as a percentage of the concentration in the 1st-min sample is plotted against time on a semilogarithmic scale and shows the rapid clearance of the isotope from the circulation. The time constant (t) of the first exponent is 9 min and that of the second exponent, 160 min.

The uptake in the tissues varies with time and is a reflection of the amount of activity of the isotope in the blood at that time. For an expression of the percentage of the injectate in the whole body, five dogs were killed and completely dissected, and the mean percentage of tissue per total body weight was calculated. From these figures was estimated the percentage of injectate in the whole body (Eq. 9). There is a 69% and a 64% drop in the radioactivity of the skin and muscle, respectively, from the 1st to the 4th h. However, the liver, kidney, lung,

and gut have only a small drop in activity over the same period, ranging from 8 to 27%. Bone uptake over the 4-h period is illustrated in Fig. 4. The mean was $23 \pm 3\%$ ($N = 11$). The apparent change from *hour 1* to *hour 4* is best explained as an experimental variable. The amount of EHDP in the urine increases from 25 to 54% by 4 h, as is shown in Fig. 4. The ratio of radioactivity calculated from Eq. 10 is demonstrated in Fig. 5. At 4h the ratio of radioactivity of bone to plasma is four times that at 1 h. This ratio reflects the background activity seen at the time of bone scanning, and although the activity in the kidney is high, the activity in the other tissues is relatively low and therefore the image of the bone will be clearer.

Renal clearance

The fractional excretion of [^{99m}Tc]EHDP, i.e., the clearance of [^{99m}Tc]EHDP divided by the clearance of inulin, in the unoperated control dogs was 30, 26, 25, and 29% with a mean $\pm$ SD of $27.3 \pm 2.0\%$. The fractional excretion of EHDP in three dogs after total thyroparathyroidectomy did not differ from control dogs, being 23, 31, and 22% with a mean of $25.3 \pm 5.0\%$. The serum calcium fell from 10 to 5 mg/dl.

In the third group, the effect of parathyroid hormone on phosphate clearance was compared with its effect on [^{99m}Tc]EHDP. The clearance for [^{99m}Tc]EHDP was similar to that in the previous experiments. The response of phosphate to parathyroid hormone is summarized in Table 3, in which the fractional excretion of [^{99m}Tc]EHDP is compared with the fractional excretion of phosphate. In the thyroparathyroidectomized dog, there is a marked increase in fractional excretion of phosphate but no real difference in fractional excretion of [^{99m}Tc]EHDP after administration of parathyroid hormone.

Discussion

The fractional mass of cortical bone in the diaphysis of the canine tibia has been shown by Cofield et al. (9) to be fairly constant: $w_c/(w_c + w_m)$ averaged 0.91 ± 0.03 . Furthermore, microscopic studies in this laboratory by Lopez-Curto have shown that the marrow of the dog diaphysis is essentially a fatty structure, providing support for the lateral branches of the nutrient artery as they enter the endosteal surface of the cortex. The vessels, before entering the cortex, are probably too large for exchange to take place. For this reason, this is a study of the movement of [^{99m}Tc]EHDP across the capillaries within the Haversian canals, using the technique of simultaneous arterial injection of diffusible and non-diffusible tracers which has been developed by Chinard et al. (7), Martín and Yudilevich (23), and Crone (12). The technique of adding a further isotope to the injection to produce a mixture of diffusible, nondiffusible, and test tracer has been developed by Crone (11). Davies et al. (13) have applied this method to bone to estimate the transcapillary exchange of strontium. The third tracer, sucrose, was used because it is inert, it penetrates the capillary wall, but it does not penetrate cells, and it has a hydrated radius of 5.4 Å.

One of the main assumptions of the single-injection technique is that there is no back diffusion of the permeant tracer into the flowing blood during the initial phase of passage of the bolus. The effect of back diffusion in the present investigation is small because of the low extraction of [^{99m}Tc]EHDP and the relatively slow circulation of blood through

diaphyseal canine bone of 1.47 ml/min per 100 g (9). The other main assumption is that the extravascular space is large enough for diffusion of the sucrose to occur. The presence of an extravascular space has been demonstrated by electron microscopy (32), by using Thorotrast (28), and by estimating extravascular mineral concentration in bone (6). Owen et al. (24) have calculated the bone tissue fluid to be 135 μ l/g of wet bone in rabbits, and the total water space of cortical bone has been estimated from desiccation experiments to be from 0.15 to 0.26 g/ml in dogs (20). Lopez-Curto et al. (22) have shown the average ratio of extravascular sucrose space to intravascular space in cortical bone to be 3.6. Mathematical modeling (1) suggests that the extravascular-extracellular space is large enough to minimize early tracer return.

The permeability ratio of [^{99m}Tc]EHDP to the freely diffusible sucrose was 0.71, which is similar to the calculated ratio of free diffusion coefficient of [^{99m}Tc]EHDP to sucrose, 0.78. This suggests that the mechanism for transcapillary exchange of [^{99m}Tc]EHDP across the capillary in bone is by passive free diffusion.

Davies et al. (13), in this laboratory, have shown that ^{85}Sr moves by free diffusion across the bone capillary and have confirmed that this is the predominant mechanism for transcapillary exchange by studying the movement of the negatively charged ion ^{18}F and the lipid-soluble molecule antipyrine. [^{99m}Tc]EHDP is a much larger molecule than the others that have been studied, and its low extraction is related to the effect of its size on its passage through the transcapillary clefts. The width of these clefts has been estimated by electron microscopy in muscle to be 40 $\text{\AA}$ (19). The E_{max} for EHDP was similar to that of pyrophosphate, a compound with a proposed molecular weight of 298 (5), but was a good deal lower than that of ^{85}Sr , which is a small molecule with a hydrated radius of 4.2 $\text{\AA}$ (26). We found that E_{max} and E_{net} for strontium were similar to previously reported results (Table 2).

[^{99m}Tc]EHDP is rapidly cleared from the blood, particularly within the first 20 min. *It* has been reported that the blood levels of [^{99m}Tc]EHDP decreased over a period of time and the urine level increased. Hughes et al. (16), investigating phosphate compounds in rabbits, demonstrated the rapid blood clearance of EHDP compared with that of pyrophosphate or tripolyphosphate. The rapid blood clearance of EHDP compared with that of polyphosphate or pyrophosphate has been confirmed in patients who have undergone bone scanning to detect metastases from breast tumors (8).

The percentage uptake in the organs varies, and whereas the bone uptake is relatively constant at between 20 and 30% of the initial dose over the 4-h period, the tissue and blood levels decrease and the urine excretion increases. The total bone uptake occurs in the first few minutes and then the blood level falls with time and the urine level rises. The percentage radioactivity in the tissue varies, being highest in the 1st h and lowest by 4 h. The ratio of radioactivity of tissue to that of plasma is highest for bone at 4 h. This would suggest that a time after 3 h might be the most favorable for a bone scan, fully recognizing that these are experiments in a dog model. This rapid blood clearance of [^{99m}Tc]EHDP has been confirmed in patients (14).

The renal clearance of [^{99m}Tc]EHDP was found to be less than that of [^{14}C]inulin in all three groups studied, controls, thyroparathyroidectomized dogs, and thyroparathyroidectomized animals given parathyroid hormone. We did not find any difference, however, in the clearance of [^{99m}Tc]EHDP compared with that of inulin after total thyroparathyroidectomy or after parathyroid infusion, although in the same experiment the phosphate excretion was influenced by the parathyroid hormone. Becker et al. (3), after giving EHDP without the ^{99m}Tc to male volunteers, could not find any influence of parathyroid hormone control on this compound.

[^{99m}Tc]EHDP is now generally available for bone scanning and can be used repeatedly without major risks to the patient. Its advantage is that it will allow regular follow-up of patients, particularly with regard to diagnosis, to response or resistance to treatment, and to the general study of the diseases of bone.

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Fig. 1.

Examples of outflow dilution curves, from one dog, of albumin, sucrose, and EHDP following a 47-s injection into nutrient artery (*upper*) with extraction derived from Eqs. 2 and 5 (*lower*).

Fig. 2.

Examples of outflow dilution curves, from one dog, of albumin, EHDP, and strontium to demonstrate greater extraction of smaller molecule strontium.

Fig. 3.
Example of a plasma clearance curve for EHDP over 4 h, showing rapid plasma clearance.

Fig. 4. Mean percentage of injectate in various tissues of the body at 1, 2, 3, and 4 h, showing decreasing blood, increasing urine, but constant bone uptake.

Fig. 5.
Mean ratios of radioactivity of tissue to that of plasma at 1, 2, 3, and 4 h, from Eq. 10.

Table 1

Extraction of [^{99m}Tc]EHDP

$\frac{[^{14}\text{C}]\text{Sucrose}}{E_{\text{max}}}$		$\frac{[^{99m}\text{Tc}]\text{EHDP}}{E_{\text{max}}}$		Permeability Ratio
E_{max}	E_{net}	E_{max}	E_{net}	
0.49	0.13	0.32	0.17	0.57
0.30	0.00	0.25	0.12	0.81
0.28	0.01	0.26	0.15	0.92
0.36	0.18	0.24	0.14	0.61
0.41	0.17	0.22	0.18	0.47
0.41	0.10	0.24	0.15	0.52
0.33	0.15	0.25	0.19	0.72
0.26	0.09	0.25	0.17	0.96
0.48	0.23	0.37	0.24	0.71
0.31	0.32	0.25	0.27	0.78
Mean	0.36	0.14	0.27	0.71
$\pm\text{SD}$	± 0.08	± 0.09	± 0.05	± 0.16
N	10	10	10	10

Table 2

Comparison of extraction

	$E_{\max}$	E_{net} (3 min)
<i>Present study</i>		
$[^{99\text{m}}\text{Tc}]\text{EHDP}$	0.27 ± 0.05	$0.18 \pm 0.05^*$
	($N = 10$)	($N = 10$)
$[^{99\text{m}}\text{Tc}]\text{pyrophosphate}$	0.43 ± 0.08	$0.36 \pm 0.1^\dagger$
	($N = 4$)	($N = 4$)
^{85}Sr	0.75 ± 0.1	0.67 ± 0.1
	($N = 3$)	($N = 3$)
<i>Earlier studies</i>		
^{85}Sr (10)		0.76 ± 0.06
		($N = 10$)
^{85}Sr (9)	0.53 ± 0.08	0.41 ± 0.06
	($N = 12$)	($N = 12$)
^{85}Sr (13)	0.69 ± 0.1	0.56 ± 0.1
	($N = 14$)	($N = 14$)

Values are means $\pm$ SD.

* At 5 min.

† At 2 min.

Table 3

Response of phosphate to parathyroid hormone

Expt	No. of Clearance Periods	C _{EHDP} , ml/min	C _{PO₄} , ml/min	C _{in} , ml/min	C _{EHDP} /C _{in}	C _{PO₄} /C _{in}	Plasma [^{99m} Tc]EHDP, cpm/ml × 10 ⁻³ *	Plasma PO ₄ , mM
Thyroparathyroidectomy	3	30.6 ± 1.1	0.20 ± 0.06	77.8 ± 4.4	0.39 ± 0.03	0.003 ± 0.0008	0.093 ± 0.005	2.25 ± 0.02
Parathyroid infusion	3	21.2 ± 6.3	3.90 ± 1.20	46.1 ± 3.2	0.46 ± 0.11	0.090 ± 0.03	0.131 ± 0.004	2.41 ± 0.08
Thyroparathyroidectomy	3	26.8 ± 0.43	2.90 ± 0.2	58.3 ± 3.9	0.46 ± 0.03	0.049 ± 0.002	0.050 ± 0.001	1.92 ± 0.07
Parathyroid infusion	10	32.8 ± 2.2	13.0 ± 0.9	64.7 ± 2.3	0.51 ± 0.04	0.200 ± 0.02	0.073 ± 0.003	2.60 ± 0.09
Thyroparathyroidectomy	2	33.5 ± 12.5	0.45 ± 0.11	47.0 ± 7.0	0.71 ± 0.16	0.009 ± 0.001	0.070 ± 0.140	1.66 ± 0.02
Parathyroid infusion	8	28.6 ± 3.8	13.5 ± 1.5	57.2 ± 4.9	0.49 ± 0.04	0.250 ± 0.03	0.085 ± 0.400	1.82 ± 0.05

Values are means ± SD.

* Normalized to the fraction of the injectate.