INVESTIGATIVE NUCLEAR MEDICINE

Studies in Skeletal Tracer Kinetics. V: Computer-Simulated Tc-99m(Sn)MDP Bone-Scan Changes in Some Systemic Disorders: Concise Communication

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Using compartmental analysis techniques, we modeled the biodistribution of Tc-99m(Sn)methylene diphosphonate in humans on a computer, and by selectively perturbing appropriate rate constants, we simulated changes in contrast between bone and soft tissue in a number of systemic disorders. The model predicts low contrast in patients with moderate to marked edema, obesity, congestive heart failure, or decreased cardiac output states and high contrast with as little as 25% increase in bone avidity for the tracer. In acute renal failure without fluid-volume imbalance, image contrast should be normal. The model predicts greater contrast shortly after injection in patients with increased cardiac output, skeletal blood flow, or bone avidity; images made at these times would be indistinguishable. These simulations are in keeping with reports in the literature of bone images and bone-to-soft tissue ratios in many of these conditions, suggesting that modeling studies could play an important role in image interpretation.

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We have shown that the kinetics of the skeletal tracers F-18 fluoride and Tc-99m(Sn)methylene diphosphonate (Tc-99m MDP) can be described by the methods of compartmental analysis and modeling, using computer simulation techniques (*1*,*2*). By appropriate choice of model parameters, changes in scintigraphic characteristics, such as target-to-background (bone-to-soft tissue) contrast, counting rate, and a statistical figure of merit can be depicted for normals as a function of time (*2*). We have also shown that perturbation of the intercompartmental rate constants can simulate changes in cardiac output, skeletal blood flow, and bone formation rate, with respect to F-18 fluoride kinetics in humans (*1*).

In this study we applied these methods to simulate Tc-99m MDP bone-scan alterations in a variety of systemic disorders. We were particularly interested in the effects on scan contrast of changes in cardiac output, skeletal blood flow, edema, renal failure, and bone formation rate (avidity).

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METHODS

The details of patient selection, data collection, and computer analysis have been published (*1*,*2*). Briefly, blood samples were obtained at frequent intervals for an hour, beginning 1 min after injection of Tc-99m MDP, in four normal adults aged 47–73. The data were analyzed by an iterative least-squares best-fit program, SAAM-25, after analog computer initialization, assuming a five-compartment model (Fig. 1). The output of the program is the intercompartmental rate constants k_{ji}, reflecting fractional transfer of substance per unit time from compartment i to compartment j. The rate constants where then used in a minicomputer program to generate the Tc-99m MDP content (as percent of administered dose) of each compartment in the model up to 4 hr after injection. In order to simulate the actual counting situation more closely, we did not correct for radioactive decay. For the purpose of this study, contrast

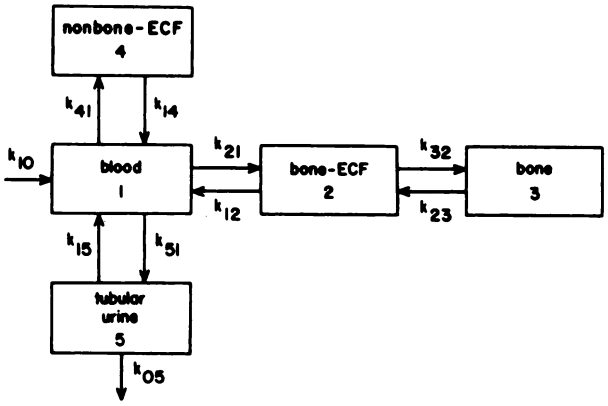

FIG. 1. Five-compartment model of Tc-99m MDP kinetics. Inter-compartment rate constants, k_{ji}, are shown.

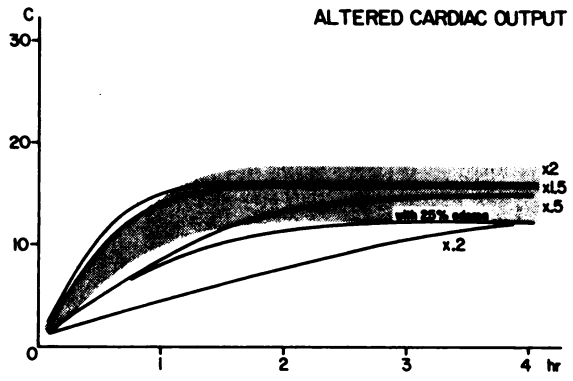

FIG. 3. Contrast as a function of cardiac output. Simulation of outputs from 20–200% of normal, with and without edema. With very low cardiac output, delayed images seem advisable.

was defined as the ratio of the concentrations in bone and soft tissue, with no effort made to simulate scatter or to include a variable fraction of the background counts into the target counts. Details are given in the earlier publication (*2*).

We simulated five pathological states in the following manner. *Cardiac output* can be shown to be the product of blood volume and the sum of the egress rate constants from blood ($k_s = k_{21} + k_{41} + k_{51}$) (*3*). To double the cardiac output, for example, we doubled k_s, and also doubled the return constants k_{12},k_{14},k_{15}, in order to keep relative volumes unchanged (*4*). The values of the other ks were not altered. *Skeletal blood flow* is calculated by k_{21}/k_s; in perturbations, k_{12} was also changed to keep k_{21}/k_{12} (bone ECF space) constant. *Edema* was simulated by decreasing k_{14} in order to increase the ratio k_{41}/k_{14}, and therefore the relative non-bone ECF space, without altering flow. To simulate congestive heart failure (decreased cardiac output with edema), we first decreased k_s and then lowered k_{14} more than required to maintain volume. For *renal failure*, k_{51} was set to zero. *Bone avidity* was altered by changing k_{32}.

Results were displayed graphically, comparing each perturbation with the range of ±20% about the mean of the normal contrast curve.

RESULTS

The bone-to-soft tissue contrast for normals is shown in Fig. 2, together with the ±20% range. After 2 hr, contrast increases very slowly and becomes constant at 6 hr.

Changes in cardiac output between 0.5 and 2 times normal appear to have no effect on scans performed later than 2 hr after injection (Fig. 3), but a markedly decreased output (0.2 × normal) will give a low-contrast image. Minimal to moderate congestive heart failure (output 0.5 × normal with 25% edema, equivalent to about 3.5 liters of fluid) does not affect the scan. In the first 30 min after injection, however, a 50% increase or decrease in cardiac output is detectable. Edema of at least 25% appears to be required to affect the scan (Fig. 4).

Changes in skeletal blood flow between 0.5 and 2 times normal do not affect the scan after 2 hr, but would be detectable early (Fig. 5). Interestingly, a very low skeletal blood flow may give a high-contrast image.

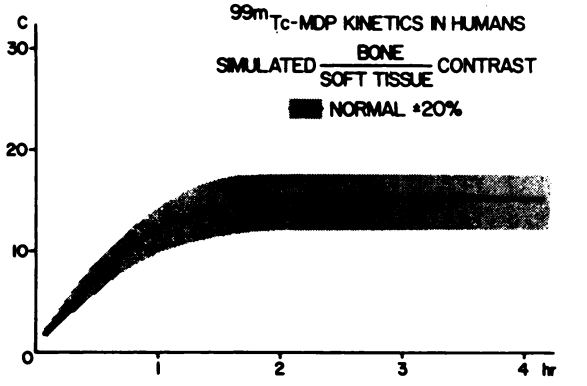

FIG. 2. Bone-to-soft tissue contrast (C) in normal persons as function of time. Shaded area gives the range, ±20%, and appears on subsequent figures.

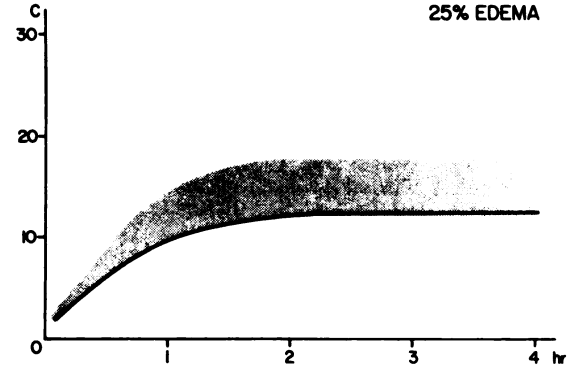

FIG. 4. Less than 25% expansion of ECF (edema, obesity) should not affect contrast.

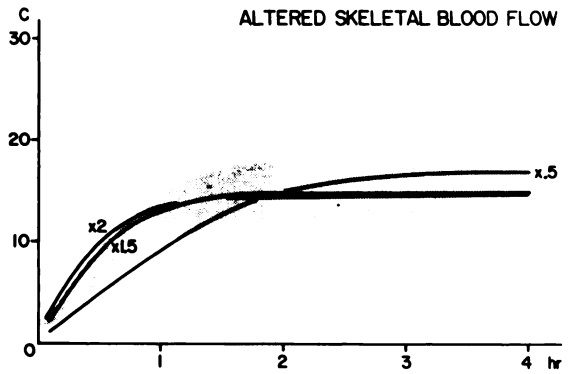

FIG. 5. An increase in skeletal blood flow produces relatively high contrast in an early image, but scans made several hours after injection appear normal.

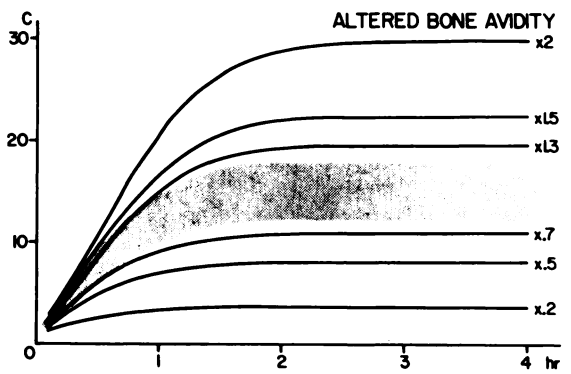

FIG. 7. Altered bone avidity affects contrast almost linearly. As little as a 25% increase should be detectable in images. Note that contrast may also be increased in early images.

Acute renal failure is seen to have no effect on image contrast (Fig. 6), but when accompanied by moderate edema would give a low-contrast study. Chronic renal failure with >40% increased bone formation rate (as in secondary hyperparathyroidism) would produce a high-contrast image.

Altered bone avidity affects the scan markedly, and almost linearly. Changes in bone formation rate of as little as ±25% appear to be detectable by scanning, at 2 or more hr after injection. More marked changes are detectable early (Fig. 7).

DISCUSSION

These computer simulations provide a useful guide for improving bone-scan interpretations. In the few instances in which correlative information is available, the simulations appear to predict correctly the scintigraphic findings. Expansion of the extracellular fluid space, as in edema (both generalized and localized) or obesity, has been reported to diminish the bone-to-soft tissue contrast (*5*), as is predicted by the model. As little as 3.5 l of fluid should be detectable. This effect is independent of any contrast alteration resulting from photon absorption secondary to increased tissue mass, as had been suggested (*6*).

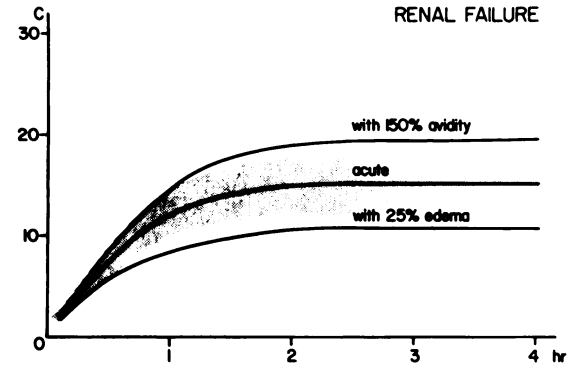

FIG. 6. Acute renal failure without volume imbalance gives normal images, but concurrent edema or osteodystrophy should be identifiable.

According to the model, acute renal failure should produce a bone scan with normal contrast, and this indeed is the case (*7*). Chronic renal failure, on the other hand, should have two opposing effects: (a) decreased contrast from ECF expansion, and (b) increased contrast from renal osteodystrophy. Both of these effects have been reported, in terms of altered bone-to-soft-tissue ratios (*8–10*), as well as image appearance (*7,11*), and the combination of the two (*12*). The increased contrast found in the majority of patients with chronic renal failure (*7*) and renal osteodystrophy (*8*)—and almost invariably in patients with secondary hyperparathyroidism (*11,13*) or on dialysis (*10,11*)—is inversely related to the glomerular filtration rate (*7*) and is proportional to serum and/or urinary hydroxyproline concentration (*10*). A relationship to serum alkaline phosphatase has been suggested (*11*), but not confirmed (*13*).

Primary hyperparathyroidism has been reported to increase the bone-to-soft tissue ratio in only a minority of patients in most series (*8,10,13*), and scans are usually normal, except for the hands (*14*). Whole-body retention of tracer, on the other hand, is uniformly increased in this condition, with a direct correlation claimed between it and the level of serum immunoreactive parathyroid hormone (*15*). Osteomalacia (e.g., vitamin D deficiency), however, gives rise to an increased bone-to-soft-tissue ratio in most patients (*7,15*) as a result of increased bodily retention and skeletal uptake of the tracer (*9*). In patient evaluation studies using a model smaller than ours, Caniggia and Vattimo found a 100% increase in bone avidity, on the average, and increased whole-body retention of Tc-99m MDP in patients on chronic hemodialysis or with primary hyperparathyroidism or osteomalacia (*9*). These findings are all in keeping with our simulation studies, which suggest that an increase in bone formation rate by as little as 25% should be detectable by scanning.

In contrast to these disorders, little clinical information is available concerning scintigraphic abnormalities in states of altered blood flow. The simulations suggest

that an increase in cardiac output or in skeletal blood flow is undetectable by bone scanning, 2 hr or more after tracer injection. Except for hyperthyroidism, which is associated with an increase in bone formation rate (*16*), there are no reports, to our knowledge, of a generalized increase in bone-to-soft tissue contrast in states with high cardiac output, and the only abnormalities regularly seen in these conditions are of a focal nature (e.g., Paget's disease, resolving sickle-cell infarct, etc.). The model predicts that mild to moderate congestive heart failure (cardiac output 50% normal, with 25% edema) would also probably not be detectable on scan, but that a marked drop in cardiac output would result in a low-contrast study. This may be the cause of the low-contrast ("technically poor") Tc-99m pyrophosphate images sometimes seen soon after an acute myocardial infarction.

In contrast, the simulations suggest that early images—up to 30 min after tracer injection—will show contrast alterations for changes in blood flow greater or less than 50% of normal, both for systemic flow (cardiac output) and skeletal flow. This is nonspecific, however, since equivalent changes in bone avidity will have the same effect. Although our model is not directly applicable to focal disease, strictly speaking, it provides support for the so-called immediate/delayed imaging method ("blood-pool/bone imaging") for distinguishing cellulitis from osteomyelitis (*17*); i.e., an abnormal early image can be found in either disorder, but an abnormal delayed image is the result of new bone formation (osteomyelitis).

An important finding emerged from this study with respect to the interval between dose injection and imaging of the patient with low cardiac output, e.g., in moderate to severe congestive heart failure. In this situation, contrast is well below the normal range until about 4 hr after injection. If the simulation analysis can be confirmed clinically (we are unaware of any published data on this point), then images in these patients should be delayed until about 4 hr after injection of the Tc-99m MDP.

The term *contrast* as used in this study differs from the "bone-to-soft tissue ratio" in common clinical use in that the numerator does not include a background contribution, and therefore direct comparison with computer regions of interest (ROI) is not feasible. It is also different from the term as used by physicists to describe modulation transfer function, for example, $(T - B)/(T + B)$, or in a statistical sense $(T - B)/(T^2 + B^2)^{1/2}$, where T and B are target and background counts. The latter expression was used by Mallard and Corfield to evaluate the significance in counting-rate density (*18*), and we used their approach to estimate the range of normal contrast expected in a clinical situation. Assuming 400,000 counts per image, collected by a 15-in. sodium iodide crystal, and a target-to-background contrast of 15:1, then an area of increased count density the same size as the target and background would have to contain 14% more counts than the (normal) target in order to be seen, assuming three standard deviations for significance. These conditions are ideal, however, and in practice the target-to-background ratio is lower because of scatter and geometric factors (*8,10,13,15*), or a smaller camera may be used, or the area of abnormal bone may be smaller, etc., all of which increase the minimum counting-rate increase required for detectability. We therefore chose 80–120% of normal as the limits of the normal range of target-to-background contrast on which to base the analysis. This value, ±20% of normal, is in general clinical use.

Note that the values for the normal intercompartmental rate constants in the model are based on studies in older adults, and perturbations of this model do not necessarily reflect identical quantitative changes in younger persons. In any case, the model predictions are amenable to testing. Particularly interesting are the simulated contrast values expected for increased bone avidity (viz., hyperparathyroidism), altered cardiac output, and edema, since quantitative measures of these conditions are available for rigorous analysis and comparison.

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