A Comparison of Skeletal Uptakes of Three Diphosphonates by Whole-Body Retention: Concise Communication

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Twenty normal volunteers had measurements of 24-hr whole-body retention (WBR) of three structurally related Tc-99m-labeled phosphonate skeletal imaging agents: (1-hydroxyethylidene) diphosphonate (HEDP), methylene diphosphonate (MDP), and hydroxymethylene diphosphonate (HMDP). The average WBR values, reflecting skeletal uptake, were 18.4, 30.3, and 36.6%, respectively. These results clearly illustrate that slight alterations in diphosphonate molecular structure have a significant effect upon specificity for osseous tissue, and thus may affect skeletal image quality and the usefulness of the WBR technique in diagnosing metabolic bone disease.

J Nucl Med 22: 880–883, 1981

The development of skeletal imaging agents has been focused around structural modifications of the methylene diphosphonate (MDP) molecule. The addition of the hydroxyl group to the central carbon atom of MDP to produce hydroxymethylene diphosphonate (HMDP), or an additional methyl group to the hydroxylated central carbon atom to produce 1-hydroxyethylidene diphosphonate (HEDP), have been shown in vitro and in animal studies to produce significant differences in both the pharmacokinetics and osseous specificity of the agents (*1–4*).

Clinically, the accurate comparative quantitation of skeletal uptake at times shortly after administration of the skeletal imaging agents presents a number of technical problems that can be circumvented by using the 24-hr whole-body retention (WBR) technique (*5*). In this paper, the WBR values for the three structurally similar diphosphonates HEDP, MDP, and HMDP (Fig. 1), were all compared in 20 normal subjects to assess the relative skeletal affinities of these agents. The clinical utility of the differences in absolute skeletal uptake has implications for skeletal image quality, the time required to obtain images, and the use of the WBR technique in diagnosing metabolic bone disease.

Received Mar. 26, 1981; revision accepted June 11, 1981.

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METHODS AND MATERIALS

Twenty normal volunteers (age range 22–65 yr, mean 40.2) had 24-hr WBR measurements following intravenous injections of Tc-99m-labeled HEDP, MDP, and HMDP. All three were prepared according to manufacturer's instructions with the exception of the activity level, which was only 50 μCi per dose. The whole-body count was measured at 5 min and again at 24 hr after injection, using a standard shadow-shield whole-body monitor (*5*). Twenty-four-hour WBR values for the three agents were calculated, after appropriate background subtraction, by taking the 5-min count as 100% and correcting for radioactive decay. The WBR measurements were performed at least one week apart, with 17 of the 20 triple studies falling within a 2-mo period. The remaining three studies were over a 3- to 4-mo period.

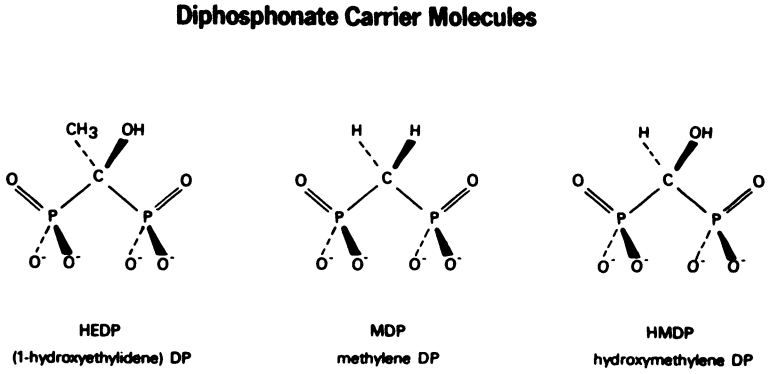

FIG. 1. Unprotonated structures of HEDP, MDP, and HMDP.

This study uses a randomized block design wherein each subject was treated with each of the three agents studied. Therefore, the data were analyzed using analysis of variance for randomized blocks (*6*). Comparisons of HMDP with each of the other agents were done using the *t*-distribution procedure described in Sec. 23.4 of Ref. 6.

RESULTS

The absolute whole-body retention values for each of the 20 normal volunteers are given in Fig. 2. Tests of difference for the three treatments in the individuals are highly significant ($P < 0.001$). As shown in Fig. 3, the mean WBR and standard deviation values for HEDP, MDP, and HMDP are 18.41% ± 2.94, 30.30% ± 4.16, and 36.55% ± 5.0, respectively. The WBR values ranged from 12.89–22.45% for the HEDP agent, 23.22–36.4% for the MDP, and 25.07–44.23% for the HMDP. Thus the mean WBR of HMDP is about double that of HEDP, and is 20% greater than that of MDP. The differences, at 95% confidence interval, between the HMDP and HEDP agents, and the HMDP and MDP agents, are 18.2% ± 1.2 and 6.3% ±1.1, respectively. The small standard deviations of the differences reflect the fact that results for individual subjects are in closely similar order for the three agents (Fig. 2). In other words, even within this control group, individual small differences are demonstrated similarly by the three agents.

The quantitative differences between HEDP and MDP are in excellent agreement with WBR values previously reported for a small group of subjects (*7*).

DISCUSSION

In theory, high skeletal uptake of tracer is desirable for bone scanning, since this may allow clearer delineation of the skeleton and minimize the time required to perform a study. At present there are no reports of significant differences between HEDP, MDP, and HMDP when used for the detection of metastatic disease—i.e.,

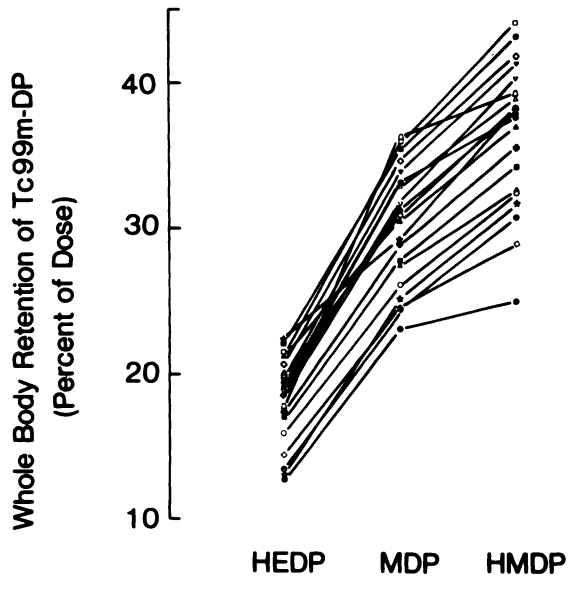

FIG. 2. Repeat 24-hr measurements of whole-body retention using Tc-99m HEDP, Tc-99m MDP, and Tc-99m HMDP skeletal imaging agents in 20 normals.

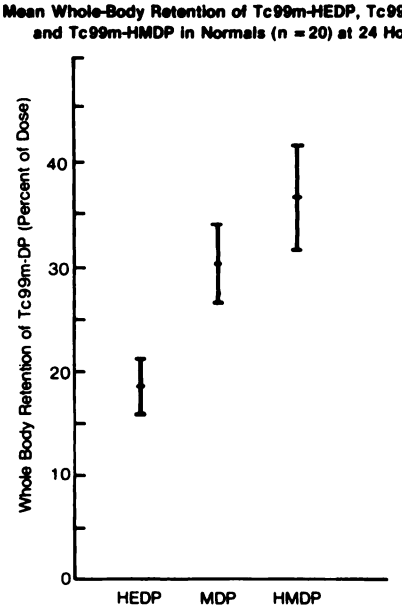

FIG. 3. Mean 24-hr values, with standard deviation, for whole-body retention of Tc-99m HEDP, Tc-99m MDP, and Tc-99m HMDP.

increased skeletal uptake of tracer is not necessarily advantageous for lesion detection—and indeed we have previously suggested that where there is high uptake of tracer by normal bone, lesions may even be less clearly visualized (*7*). However, in a recent comparison between the lowest-uptake agent, HEDP, and the highest, HMDP, this was not found to be the case (*8*). In the studies where images obtained at both 2 and 4 hr after injection with either HEDP or MDP have been compared, a significant improvement in image quality was seen at the later time (*9,10*). It therefore appears that while bone scans using HEDP and MDP can provide satisfactory diagnostic information at 2 hr after injection, the quality of such images might be considered poor and perhaps even unacceptable by current standards. Image quality is principally related to the absolute retention of the skeletal imaging agent on bone and the time available to allow the soft-tissue tracer component to be excreted by the kidneys. The diagnostic quality of images obtained with HMDP at scanning times earlier than 4 hr after injection has still to be established.

Whereas differences in diphosphonate uptake at 24 hr cannot necessarily be extrapolated to routine clinical scanning times, the validity of the 24-hr value is clinically supported by Khedkar et al., who quantitated MDP and HMDP bone uptake in the pelvic bones of 12 patients and showed higher skeletal retention of HMDP at 0.5, 3, and 24 hr (*11*). Similar quantitative differences between MDP and HMDP were obtained by Bevan et al. (*3*) at 1.5 hr in beagle dogs, a model we feel can be extrapolated to humans.

The exact mechanism of diphosphonate uptake in bone is as yet incompletely understood (*12*), but a common factor for all three agents is the ability of the diphosphonate to coordinate with technetium, with subsequent sorption of the tracer onto bone (*13*). The 20% differential in WBR value between MDP and HMDP is most probably related to differences in the bridging (binding) between the agents and hydroxyapatite, primarily the postulated bidentate-bidentate binding for nonhydroxy molecules such as MDP and bidentate-tridentate binding for molecules with a hydroxy group such as HMDP (*2,13*). Kinetic studies by Arnold et al. (*14*) suggest that such variations in molecular structure do affect osseous affinity and lead to tighter binding of HMDP and subsequent higher retention on bone. Less understood is the dramatic difference observed between HEDP and HMDP, both capable of bidentate-tridentate binding. Increased steric hindrance associated with the methyl group on the central carbon atom, differences in solubility, and differences in molecular size as well as in the diphosphonate polymeric complexes themselves have all been suggested (*2,4,13*).

This study has possible implications relating to the use of (a) different diphosphonates for bone scanning, and (b) WBR in the evaluation of patients with metabolic bone disease. Whereas in metastatic disease focal abnormalities are seen on the bone scan, in metabolic bone disease the skeleton is usually diffusely involved by the metabolic process and typically focal abnormalities are absent. An awareness of abnormality then depends upon a subjective impression of increased tracer uptake throughout the whole skeleton. With HEDP several metabolic features have been recognized on the scan, and these have allowed differentiation of various metabolic bone disorders from a control population (*15*). In the case of either MDP or HMDP, the higher absolute uptake relative to HEDP raises the possibility that it will be more difficult to identify a metabolic process against this higher background of normal skeletal uptake. Where 24-hr WBR of diphosphonate is used to identify patients with increased skeletal metabolism (*5,16–18*), HEDP, with its tighter normal range at lower absolute skeletal uptake, would seem to be the agent of choice, since it provides a wider range in which to detect abnormality with less overlap between normal and abnormal.

ACKNOWLEDGMENT

We thank Mrs. Elizabeth Scott for her careful whole-body retention measurements.

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