Human Pharmacokinetics of Samarium-153 EDTTMP in Metastatic Cancer

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Samarium-153 ethylenediaminetetramethylene phosphonic acid (\[^{153}\text{Sm}\]EDTMP) has been proposed to palliate pain resulting from osteoblastic metastatic bone cancer. Encouraging results in dogs with primary malignant bone cancer provided the catalysis for human biodistribution studies in five patients with metastatic skeletal carcinoma. The objective was to assess the preferential localization of \[^{153}\text{Sm}\]EDTMP in bony lesions and compare it to the \[^{90}\text{Y}\]To-labeled phosphonates. Blood clearance of \[^{153}\text{Sm}\]EDTMP was rapid with minimal accumulation in nonosseous tissues. Both radiopharmaceuticals showed identical lesion uptake in 23 paired lesions (p > 0.05). This indicates that the two radiopharmaceuticals concentrate in metastatic skeletal lesions by the same mechanism and since \[^{153}\text{Sm}\]EDTMP emits beta radiation it may be therapeutically useful in ameliorating metastatic bony cancer pain.


To palliate intractable skeletal pain due to disseminated bony metastases, several radiotracers have been used with none achieving widespread clinical acceptance. Phosphorus-32 as Na,\[^{32}\text{PO}_4\], was the first and most widely employed radiotracer to treat metastatic bone cancer pain (1–6). Because of undesirable myelosuppression it has generally been abandoned. Recent reports have suggested an array of radiotracers to irradiate diffuse skeletal metastases such as rhenium-186 (\[^{186}\text{Re}\]) (7), yttrium-90 (\[^{90}\text{Y}\]) (8) and iodine-131- (\[^{131}\text{I}\]) labeled diphosphonates (9–10), and strontium-89 (\[^{89}\text{Sr}\]) chloride (11–12). At the University of Missouri-Columbia, in conjunction with the Dow Chemical Co., we have developed samarium-153 ethylenediaminetetramethylene phosphonic acid (EDTMP), a radiopharmaceutical that is chemically and biologically stable and preferentially concentrates in skeletal metastases (13–15). The short half-life of \[^{153}\text{Sm}\] (46.3 hr) makes it suitable for repeat tumor irradiation and preliminary work has shown that the chelate is effective against primary bone neoplasm in dogs (16). Before instituting a dose tolerance and therapeutic efficacy clinical trial, we evaluated this agent in humans with metastatic bone cancer using a sub-therapeutic dose of \[^{153}\text{Sm}\]EDTMP in a pharmacokinetic trial.

METHOD

Patient Selection

Five patients with histopathologically proven primary cancer and radiographic and/or scintigraphic bony metastases were studied under physicians IND 27865 (RAH). All subjects were male and their ages ranged from 62–85 yr (mean 67 ± 10 yr). Three patients had primary lung carcinoma and the other two prostate carcinoma.

Preparation of \[^{153}\text{Sm}\]EDTMP

Samarium-153 was produced at the University of Missouri Research Reactor (MURR) by thermal neutron irradiation of enriched (99.06%) \[^{153}\text{Sm}\]oxide. The oxide target was then dissolved in 1.0 N HCl and diluted to 0.1 N HCl with sterile water. Six milliliters of the solution were added to a lyophilized kit containing 210 mg of EDTMP and sufficient NaOH was added to bring the final product to a pH of 7.0–8.5. The yield of the \[^{153}\text{Sm}\]EDTMP complex was >99% determined by ion exchange chromatography (13–14). The chelate preparation can be stored in the formulation vial at room temperature and retains its stability for > 7 days. The primary radiation emissions of Sm-153 are shown in Table 1, and the structure of EDTMP is shown in Figure 1.
TABLE 1
Primary Radiation Emissions of $^{153}$Sm

<table>
<thead>
<tr>
<th>Maximum energy (keV)</th>
<th>Type</th>
<th>Abundance</th>
</tr>
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<tbody>
<tr>
<td>810°</td>
<td>Beta</td>
<td>20%</td>
</tr>
<tr>
<td>710°</td>
<td>Beta</td>
<td>50%</td>
</tr>
<tr>
<td>640°</td>
<td>Beta</td>
<td>30%</td>
</tr>
<tr>
<td>103</td>
<td>Gamma</td>
<td>28%</td>
</tr>
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</table>

*The average beta particle energy from $^{153}$SmEDTMP is 225 keV (NCRP Report No. 58, 1985) and the average range in water is 0.83 mm (33).*

Biodistribution

After injecting 2 mCi of $^{153}$SmEDTMP intravenously, whole-body planar scintigraphic images, blood clearance and 24-hr urinary excretion of the radiopharmaceutical were obtained using the 103 keV (29.8%) gamma photon emission of $^{153}$Sm. The images were started 2 hr following the injection of the $^{153}$SmEDTMP and a large field-of-view (FOV) scintillation camera equipped with a low-energy all purpose (LEAP) parallel hole collimator. The count data was digitized and computer enhanced to produce quality images for interpretation and quantification. The quantified indices included: lesion-to-normal bone ratios; lesion to soft-tissue ratios; and normal bone to soft-tissue ratios. The ratios were determined after the soft tissue background was subtracted. An experienced observer (AS) outlined lesions on the scintigrams with the computer (ADAC-3300) and the average regional counts were used to calculate the bone to nonbone ratios. Twenty-three (23) lesions were studied in the five patients. Each patient received a $^{99m}$TcHDP (Osteoscan-HDP, Mallinckrodt, St. Louis, MO) bone image 2 days before the $^{153}$SmEDTMP injection. This was done to identify the metastatic sites in the patients and generate scintigraphic images of the bony lesions so that they could be compared to the $^{153}$SmEDTMP images. As with $^{153}$SmEDTMP, the $^{99m}$TcHDP images were taken 2 hr postinjection of 20 mCi in one patient, 2 mCi in a second and 5 mCi in the remaining three. The $^{99m}$TcHDP dose was varied to adjust the dose to one which was similar to $^{153}$SmEDTMP, minimizing variations in image quality. Twenty millicuries of $^{99m}$TcHDP, the usual standard dose, was felt to be too large, while 2 mCi was obviously too low for an ideal comparison. Computer enhancement of the image was very helpful when the lower dose was used. Interobserver variability was eliminated since a single observer analyzed the data.

Radiopharmaceutical Safety

The safety of $^{153}$SmEDTMP was determined by using a sterile pyrogen free preparation, monitoring vital signs before and up to 1 hr postinjection of the $^{153}$SmEDTMP, by performing pre- and postinjection hematologic profiles (white cell, red cell, and platelet counts), urinalyses and serum chemistries (BUN, serum creatinine, and liver function tests). All pre-injection samples were drawn 4 hr prior to the intravenous administration and all postinjection samples were obtained within the subsequent 24 hr.

Statistical Methods

Skeletal ratios of $^{153}$SmEDTMP and $^{99m}$TcHDP were analyzed using the matched pair group design (17) which determines if a significant difference existed between the lesion localization of the two agents. A probability of $p < 0.05$ was considered significant. The same lesion in each patient served as control for the comparison. All data represents the mean ± 1 s.d.

RESULTS

In the top row of Figure 2 the skeletal images (A, B, C) taken with 5 mCi of $^{99m}$TcHDP and the same images in the lower row (D, E, F) taken with 2 mCi of $^{153}$SmEDTMP show excellent visualization of the multiple bony metastases. The ratios of the lesion quantification are tabulated in Table 2. Lesion-to-normal bone ratios for $^{153}$SmEDTMP and $^{99m}$TcHDP were 4.04 ± 2.62 and 4.01 ± 1.97, respectively. Lesion-to-soft-tissue ratios were 5.98 ± 3.18 for $^{153}$SmEDTMP and 6.87 ± 4.67 for $^{99m}$TcHDP. Normal bone to soft tissue ratios were 2.47 ± 1.01 for $^{153}$SmEDTMP and 2.44 ± 1.25 for $^{99m}$TcHDP. No significant difference between the accumulation of these two agents in bone cancer lesions was observed ($p > 0.5$). The data indicates that the same mechanism of localization exists for the $^{153}$SmEDTMP and $^{99m}$TcHDP in skeletal metastases, and the soft-tissue localization was minimal.

Whole blood clearance of $^{153}$SmEDTMP is shown in Figure 3. The percent dose in blood was derived from the blood volume estimates using the method of Nadler (18). Rapid chelate clearance results in only 5.17 ± 1.05% and 2.09 ± 0.52% of the activity remaining in whole blood at 2 and 4 hr postinjection. When the plasma is separated the percent $^{153}$SmEDTMP remaining at 2 and 4 hr postinjection were 5.2 ± 1.09 and 2.11 ± 0.38, respectively. The complex clears through the kidneys and the amount excreted into the urine at 24 hr is shown in Figure 4. These results of the $^{153}$SmEDTMP biodistribution are nearly identical, to the blood clearance properties of $^{99m}$TcHDP and $^{99m}$Tc methylene diphosphonate (MDP) (19). The pre- and postinjection hematologic profiles, serum chemistry and urinalyses demonstrated no changes in all five

![FIGURE 1](image.png)

Structure of the EDTMP compound which complexes with $^{153}$Sm to form $^{153}$SmEDTMP.
patients. Vital signs did not vary following the injection of \(^{153}\text{Sm}\)EDTMP indicating the safety of \(^{153}\text{Sm}\)EDTMP at the subpharmacologic doses employed in our patients.

**DISCUSSION**

Painful disseminated bony metastases are common with carcinomas of the lung, prostate, and breast. In lung cancer, bony metastases are found in 36% of patients undergoing metastatic skeletal surveys with bone scans, while nearly half of the patients with prostatic cancer demonstrate bony metastases at the time of their initial presentation (20–21). These lesions are frequently widespread and show high avidity for the \(^{99m}\text{Tc}\) phosphonate complexes. Carcinoma of the breast is the second most common cancer in females and may be associated with bony metastases in 50% of the patients within 12 mo of its initial presentation. By 18 mo bony metastases may occur in three quarters of these patients (22). Approximately one- to two-thirds of these patients will develop pain (23). External beam irradiation is an ideal therapy to ameliorate the pain of isolated metastases. Although disseminated bony metastases have also been treated with hemibody or total-body external irradiation with some success the approach of the additional radiation burden is undesirable and potentially myelosuppressive. Analgesics used to ameliorate bone pain are frequently limited in their period of effectiveness and patients rapidly develop drug tolerance. Addiction is not an uncommon sequela of narcotic analgesia in patients with intractable bone cancer pain. Pain relief using chemotherapeutic regimens and/or hormone therapy is a welcomed but unpredictable consequence and is limited and brief in duration.

For several years particulate emitting radionuclides such as \(^{32}\text{P}\) (\(T_\text{1/2} = 14\text{d};\) a pure beta emitter) as either the anionic phosphate or as a ligand (HEDP), has been used to treat metastatic bone cancer. The use of this radionuclide is complicated by excessive myelosuppres-

**TABLE 2**

Comparison of Skeletal Localization of \(^{153}\text{Sm}\)EDTMP and \(^{99m}\text{Tc}\)HDP

<table>
<thead>
<tr>
<th>Ratio</th>
<th>(^{153}\text{Sm})EDTMP</th>
<th>(^{99m}\text{Tc})HDP</th>
<th>(p^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion to bone(^1)</td>
<td>4.04 ± 2.62</td>
<td>4.01 ± 1.97</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Lesion to soft tissue</td>
<td>5.98 ± 3.18</td>
<td>6.87 ± 4.67</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Bone to soft tissue</td>
<td>2.47 ± 1.01</td>
<td>2.44 ± 1.25</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

\(^1\) All data is mean ± 1 s.d., n = 23.

\(^2\) Matched pair two group design.

\(^3\) Soft-tissue background corrected.

**FIGURE 3**

Blood clearance of \(^{153}\text{Sm}\)EDTMP. The plasma clearance curve (not shown) was identical.
URINARY ACCUMULATION OF Sm-153-EDTMP (n=5)

Mean +/- 2(Std.Dev.)

% Injected Dose in Urine vs Time (hour)

FIGURE 4
Cumulative 24-hr urinary excretion of [153Sm]EDTMP.

EDTMP has recently been reported using rat model determinations (29). The pharmacokinetic data obtained in this human study provided the base to calculate a better estimate of dosimetry for the patients receiving [153Sm]EDTMP therapy (30). Recent data from a safety study in humans performed in our laboratory (31) and in a high dose study in dogs (32) provides evidence that this agent will be able to produce desirable therapeutic effects at doses producing well tolerated transient myelosuppression. Quantitative image results demonstrated high lesion uptake with mean lesion to bone ratios of 4.04 ± 2.62 and lesion to soft-tissue ratios of 5.98 ± 3.18. The chelate clears rapidly from the plasma through the kidneys into the urine. Approximately half of the administered dose is excreted into the urine by 6–7 hr. The remaining dose (~45%) is deposited in the skeleton with little soft-tissue uptake such as the liver.

In conclusion, this study demonstrates that [153Sm]EDTMP is a suitable radiopharmaceutical to initiate therapeutic trials in patients with bone pain resulting from skeletal metastases. Its physical and biokinetics properties appear optimum and its propensity to localize in bony metastatic sites that are osteoblastic in nature has been established. Neoplastic bone disease associated with lytic-type of bony metastases such as multiple myeloma may not be treatable with [153Sm]EDTMP.

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REFERENCES