
Clinical and Clinicopathologic Effects of Samarium-153-EDTMP Administered Intravenously to Normal Beagle Dogs

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A study was undertaken to determine the degree of acute bone marrow and vital organs injury sustained when dogs were administered doses of ^{153}Sm -EDTMP calculated to irradiate an acute bone lesion arising from cancer metastasis to a dose considered palliative or even therapeutic (20–160 Gy). The study revealed significant ($p < 0.05$) temporary depression of the bone marrow in all doses in the therapeutic (>40 Gy) range. Palliative (20 Gy) doses caused significant leukocyte depression but insignificant ($p > 0.05$) depression of platelet and packed cell volumes when compared to control animals. A mild transient rise in the levels of serum alkaline phosphatase occurred immediately following radioisotope administration. All hematologic parameters had returned to normal by six weeks after the last injection of radioisotope. The study indicates potential for this compound as a safe, therapeutic radiopharmaceutical for treatment of cancer bone metastasis.

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Despite dramatic advances in the systemic treatment of cancer patients with chemotherapeutic and immunologic agents, metastatic neoplasia of bone is still a major source of pain and lifestyle disruption. More than 125,000 new cases of skeletal cancer, at least 99% of which are metastatic, are reported in the United States each year (1,2). The economic and psychologic impacts from the pain and disability of skeletal metastatic neoplasia on the individual cancer patient are major aspects of the disease.

Many patients with metastatic neoplasia of the skeleton are treated with external beam ionizing radiation, universally accepted as the most effective treatment of

bone metastasis (3). In many cases, it is not possible to attempt complete sterilization of the lesion with radiation due to the large size of the field needed and the effect that such levels of radiation would have on the late-responding or high replication rate tissues within the field (4). Therefore, the treatment is only palliative and may not substantially improve the prognosis or survival (3). The amount of time that treatment regimes require and the physical discomfort resulting from them is often such that the person has difficulty working productively or maintaining an active life style. This compounds the financial cost of the treatment as well as contributing to a poor psychological state that may have an adverse effect on the patient's survival.

Injectable radiopharmaceuticals offer the possibility of minimizing the physical, psychologic, and financial problems induced by skeletal metastatic disease without compromising treatment efficacy. Such a radioactive bone-seeking agent has several requirements. It would require minimal chemical toxicity even at relatively high dosages. The half-life should be of medium duration (~2–8 days) so as to provide the optimum radiobiologic effect. The pharmaceutical must have a very high affinity for diseased bone in relation to normal bone, minimal deposition outside the skeleton and limited concentration in the bone marrow. The mode of radioactive decay should be principally beta particle emission in order that the deposition of energy is concentrated in the immediate area of the lesion (5). Beta particles of medium energy satisfy this criteria, yet have sufficient range to penetrate into the hypoxic cell population beyond the perfusion limit of the blood. Particulate radiations also have the advantage of limiting energy deposition to the local site, thus improving the effectiveness per unit of energy deposited.

Several radioisotopes have the desired physical decay properties. Strontium-89 (^{89}Sr), rhenium-186 (^{186}Re), and phosphorus-32 (^{32}P) and several of the rare earth metal isotopes are medium-energy, beta-particle-emit-

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ting radioisotopes with half-lives of one to several days (2,6-10). Rare earth isotopes all have similar chemical properties and can be compounded with various phosphonate chelating agents to decrease their toxicity and increase their affinity for bone. The biggest problems are enhancing the lesion to normal bone ratio of deposition and limiting the effect on the bone marrow. These two problems are the major obstacle to parenteral radioisotope treatment of neoplastic skeletal diseases (7).

Samarium-153-ethylenediamine-tetramethylene-phosphonic acid (^{153}Sm -EDTMP) is one of the agents which exhibits *in vivo* localization and pharmacokinetics that are desirable for therapeutic applications and have been tested in humans (11). This isotope also has the added advantage of having a 28% abundant 103 keV gamma photon which is quite suitable for imaging by conventional gamma cameras. This permits confirmation of isotope deposition within the skeleton and allows area of interest comparisons between lesions and normal bone.

This report deals with the radiobiologic effects of ^{153}Sm -EDTMP when administered intravenously to normal beagle dogs in doses calculated to result in palliative and curative concentrations of radioactivity in neoplastic bony lesions. The dose calculations were based on experiments previously performed in rats and rabbits by our group. The percentage of injected radiopharmaceuticals concentrated in the skeleton and the lesion to normal bone ratio as determined with an acute drill hole model were used to calculate both the dose to the lesion and the normal skeleton (12,13). The percent skeletal uptake was ~56% of the injected dose and the lesion to normal bone ratio was 16:1. Our calculations based on these figures and a skeletal weight of 100 g/kg body weight for dogs indicated that an intravenously administered ^{153}Sm -EDTMP dose of 37 MBq (1.0 mCi)/kg of body weight would result in a lesion dose of ~40 Gy and a normal compact bone dose of ~250 cGy where <1% of the skeleton was involved (14).

METHODS AND MATERIALS

Samarium-153-EDTMP for injection was prepared using a sterile, pyrogen-free kit preparation at the University of Missouri Research Reactor (13). A solution of 0.1M HCl containing 185 to 1850 MBq (5 to 50 mCi) of ^{153}Sm was added to a vial containing lyophilized EDTMP with sufficient NaOH to achieve a final product pH of 7.0-8.5. The concentration of EDTMP and ^{153}Sm in the injectate was 35 mg/ml and $< 4 \times 10^{-4}$ M, respectively. The radiochemical purity, determined by the anion exchange chromatography method of Goeckeler, et al. (3), was always >99%. The ^{153}Sm -EDTMP was administered intravenously to normal unanesthetized beagle dogs. These dogs were adult, retired breeders, at least three years old obtained from a commercial colony (Marshall Research Animals, North Rose, New York). There were six dose level groups tested: 18.5 MBq (0.5 mCi)/kg body wt. one time, 37 MBq (1.0 mCi)/kg body wt. one time, 74 MBq (2.0 mCi)/kg

body wt. one time, 37 MBq (1.0 mCi)/kg body wt. once weekly for four weeks, a control group which received only a physiologic saline placebo (no drug) and a group which received a nonradioactive isotope of samarium (^{152}Sm) chelated to EDTMP. Four dogs (two females and two males) were randomly assigned to each group upon arrival. Logistical considerations prevented concurrent testing of all subjects so the animals were injected on different dates, but bias was prevented by not assigning the dogs to the dose groups sequentially. Animals from different dose groups were maintained at similar stages of the evaluation process at all times. No supportive treatment other than periodic treatment of cystitis as needed (see below) was administered to these animals during the experimental protocol.

Each animal in the study was evaluated physically, clinically and biochemically prior to injection of the samarium chelate and periodically thereafter for a period of 90 days. The evaluations included serum electrolyte and enzyme levels, blood count parameters, bone marrow biopsies, urinalysis and physical examinations. All dogs were held for a period of 16 days prior to the injection of the chelate to allow them to acclimatize to their new surroundings and recover from the stress of shipment. Any dog demonstrating abnormalities on any of the screening studies was either eliminated from the study or treated and allowed to recover (if treatment was deemed unlikely to interfere with the results of the experiment) before being injected. The most commonly encountered abnormality was bacterial cystitis which was generally responsive to non-nephrotoxic penicillin derivative antibiotics. An absence of renal toxicity was deemed important to avoid possible confusion with any nephrotoxicity which the samarium chelate, whose main path of excretion is renal, might have. Only one dog was excluded because of pre-existing medical problems.

At the end of the 90-day evaluation period, the dogs were euthanized using a sodium pentobarbital overdose and a complete necropsy examination was performed. The tissues in which significant lesions were recognized and the lesions described are listed in Table 1.

The data was analyzed using Wilcoxon's Signed Rank Test for changes from baseline within the individual groups. Due to the small number of animals in each group, significance was recognized at a p value ≤ 0.15 for this test. Response differences between the various dose groups of the experiment were evaluated using Wilcoxon Rank Sum Test. Significance was recognized at values of $p \leq 0.05$.

RESULTS

Physical Examinations

Occasionally (either before or postinjection) a dog would exhibit one or more isolated, transient temperature spikes which were not associated with any clinical abnormality such as emesis, diarrhea or a change in demeanor. In the absence of other abnormal clinical findings, these temperature spikes were attributed to excessive physical activity just prior to the temperature recorded. This was the only apparent physical abnormality observed during the study.

TABLE 1
Post Mortem Lesions in Beagles Receiving ^{153}Sm -EDTMP

Group dog I.D.	Control ABCD	Cold complex EFGH	0.5 mCi/kg IJKL	1.0 mCi/kg MNOP	2.0 mCi/kg QRST	1.0 mCi/kg \times 4 UVWX
Bone marrow			+			+
Kidneys (mineralization of collecting ducts)	+++	++ +	++++	++++	+ +	++++
Liver					+	+
Lungs				+		+
Mesenteric lymph nodes		+				+
Spleen (congestion, lymphoid depletion)	++++	++++	++++	++++	++++	++++
Testes (decrease in mature sperm count)		++				
Thyroid (follicular hyperplasia)	+	+	+	+	+	+ +
Urinary bladder (cystitis)				+		
Prostate					+	

No lesions were observed in the following organs: small intestine, skeletal muscle, ovaries, esophagus, large intestine, heart, cecum, cervical lymph nodes, brain, bone, and adrenals.

Urinalysis

Bacterial cystitis was a recurring problem in all dose groups. Some, but not all, dogs had cystitis on the basis of urinalysis at the time of arrival from the commercial supplier and others developed it during the test period. There was no association observed with the administration of either the chelate or the radioactive isotope as the cystitis was observed in all groups including the controls. This cystitis was detected on the basis of urinalysis examinations while overt clinical signs were not observed.

Serum Electrolyte and Enzyme Values

No significant alterations in any of the serum electrolyte parameters were detected in any of the groups. All groups had slight, transient rises in serum alkaline phosphatase (ALP) levels during the first few days postinjection, however, the elevation was transient and rapidly returned to normal levels (Fig. 1). These transitory rises were considered significant because they resulted in values which are considered abnormal for dogs by the UM-C Veterinary Teaching Hospital laboratory (normal range 34.0–190.0 iu). Both control and test animals were affected and no statistical evidence ($p > 0.05$) of a response difference between groups was detected during this time. Differences ($p < 0.05$) in the response between groups was detected on Day 84, however evaluation of the change scores indicated that it was the control groups, not the test animals, that changed most significantly. It is recognized that serum ALP may be elevated because of increased skeletal metabolic activity, however special isoenzyme analysis was not performed to determine whether or not the skeleton was the source of the slight elevations in the levels of this enzyme.

The serum concentration of the enzyme alanine aminotransferase (ALT), used to measure hepatocellular function, did not undergo any postinjection elevation above the acceptable normal range in any of the dose groups (Fig. 2). Mildly significant ($p < 0.15$) changes from baseline values were observed in the 18.5 MBq/kg and 37 MBq/kg \times 4 dose groups on days 28 and 56, however evaluation of response between groups revealed no evidence of significant response differences ($p > 0.05$) between any of the groups. These findings are interpreted as indicating no detectable acute damage to the liver by either the radiation or the chelating compound (EDTMP) itself. Since the liver is the second most likely organ of the body to concentrate the ^{153}Sm chelate after the skeleton (1), the lack of apparent

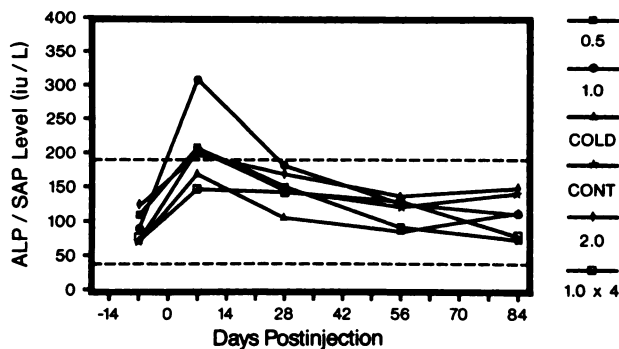


FIGURE 1
Mean serum alkaline phosphatase levels in groups of normal beagles given varying doses of ^{153}Sm -EDTMP. Dose levels administered were: (0.5 mCi (18.5 MBq)/kg, 1.0 mCi (37 MBq)/kg, 2.0 mCi (74 MBq)/kg, as single doses and 1.0 mCi (37 MBq)/kg weekly for 4 wk), in a control group and in a group given nonradioactive Sm-EDTMP complex intravenously. $N = 4$ for each group. The horizontal dashed lines indicate the extremes of the accepted normal range.

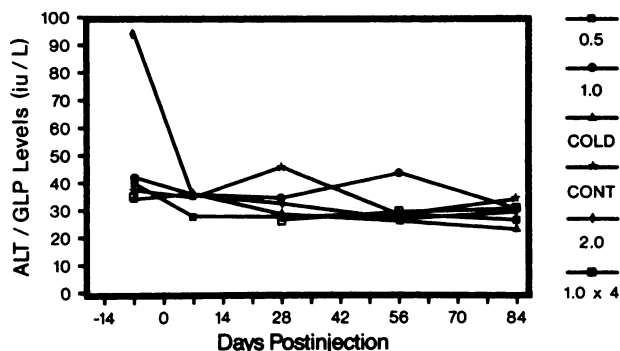


FIGURE 2
Mean alanine aminotransferase levels in groups of normal beagles given varying doses of $^{153}\text{Sm-EDTMP}$ as described in Figure 1.

hepatocellular injury in the liver was viewed as indicating that no significant acute radiation damage was incurred by the liver.

The portion of the ^{153}Sm not taken up by the bone and, to a lesser degree, other organs in the body is rapidly eliminated from the blood by the kidneys and concentrated in the urine (1). None of the animals, including those with bacterial cystitis, developed any signs, either clinical or clinico-pathologic—based on evaluation of blood urea nitrogen levels (Fig. 3)—to indicate that any detectable damage to the kidneys had occurred. No difference in the response of the blood urea nitrogen values was detected between the dose groups ($p > 0.05$). Significant changes from baseline ($p < 0.15$) occurred at the end of the study in the 37 MBq/kg and 74 MBq/kg groups, however the change was a reduction in levels, not an increase.

White Blood Cell Counts

The differential cell counts consistently indicated a decrease in the number of circulating white blood cells (WBCs) present in the peripheral blood of all dogs receiving $^{153}\text{Sm-EDTMP}$. The severity of the depression appeared to be dose related but only to a certain extent,

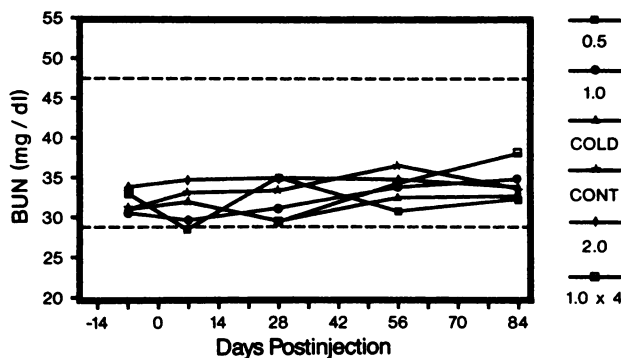


FIGURE 3
Mean blood urea nitrogen levels in groups of normal beagles given varying doses of $^{153}\text{Sm-EDTMP}$ as described in Figure 1.

as there was very little difference in the absolute minimum level attained in the two highest dose groups (Fig. 4). The drop in cell numbers began between one and two weeks postinjection in those animals which received the $^{153}\text{Sm-EDTMP}$ chelate compound. The animals which received only the non-radioactive samarium EDTMP or the saline placebo exhibited no significant ($p > 0.15$) depletion of circulating WBCs (Fig. 4). White blood cell counts generally returned to normal levels between three and four weeks postinjection, except in group six (37 MBq/kg/wk \times 4 wk) in which recovery was delayed until six weeks postinjection. Examination of the curves indicates that recovery occurred at approximately the same interval (2–3 wk) following the final injection as it did following the single injections. Statistically significant changes from baseline were detected within all of the groups receiving a radioactive compound ($p < 0.15$). However, intergroup comparisons of the change scores indicated the following: significant response differences were not detected ($p > 0.05$) between the 18.5 and 37 MBq/kg groups, the 37 and 74 MBq/kg groups differed on Days 14 and 21 only ($p < 0.05$), the 37 MBq/kg \times 4 group varied from the control and cold chelate throughout the study ($p < 0.05$), and the response of the white blood cell counts did not vary between the three lower dose rates after day 21 ($p > 0.05$).

Significant decreases in the platelet counts from baseline occurred in all of the animals which received the radioactive chelate ($p < 0.15$) (Fig. 5). The drop in platelet levels trailed the drop in WBCs slightly. The severity of the drop in circulating platelets appears dose related when viewed graphically. However, no statistical difference ($p > 0.05$) was detected in pairwise comparisons of the change scores between the 18.5 MBq and control dose groups. Although the values were significantly lower ($p < 0.05$) on Days 28 and 35 between the 37 MBq/kg \times 4 group and the other test groups, the absolute lowest value was not significantly lower ($p >$

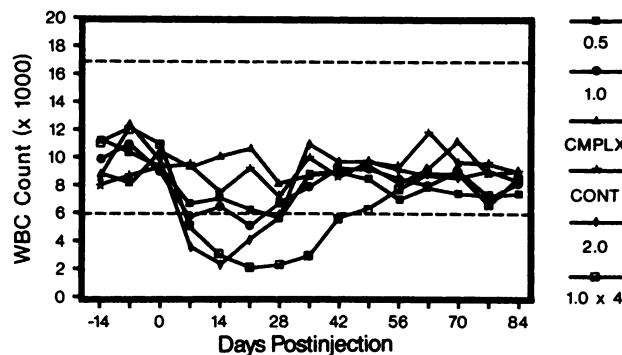


FIGURE 4
Mean white blood cell counts in groups of normal beagles given varying doses of $^{153}\text{Sm-EDTMP}$ as described in Figure 1.

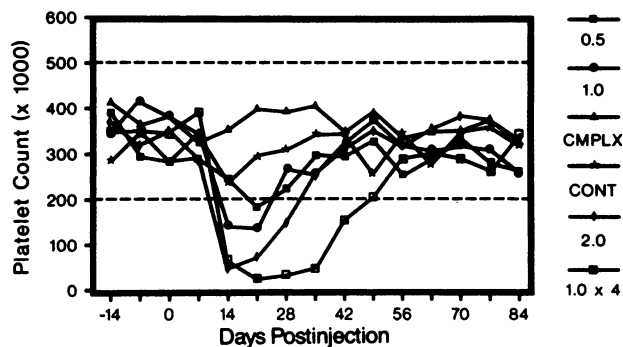


FIGURE 5
Mean platelet counts in groups of normal beagles given varying doses of ^{153}Sm -EDTMP as described in Figure 1.

0.05) than that seen in the single 74 MBq/kg dose group. No consistent difference between the change scores was noted between the three single dose groups and the control and cold complex groups after Day 28. The 37 MBq/kg \times 4 dose group did differ significantly ($p < 0.05$) from both the control and cold chelate groups until Day 77.

Although the red blood cells are also a product of the bone marrow, their longer life span apparently protected the animals from developing significant anemia. The packed cell volume counts showed a mild decrease in the higher dose groups (consistently significant only in the multidose group) at two to six weeks after the first injection, but no animal developed a severe enough response for it to be considered clinically anemic (Fig. 6). Comparison of change scores indicated that there was a difference in response ($p < 0.05$) between the 37 MBq/kg \times 4 group and the control and cold complex groups throughout the study. No pattern of alteration between the single dose groups and the cold and control groups could be established statistically.

The evaluation of damage to bone marrow was based on repeated counts of the various blood cell types present in the peripheral blood and examination of sequential bone marrow biopsies and aspirates. The bone marrow in the proximal end of the femoral and

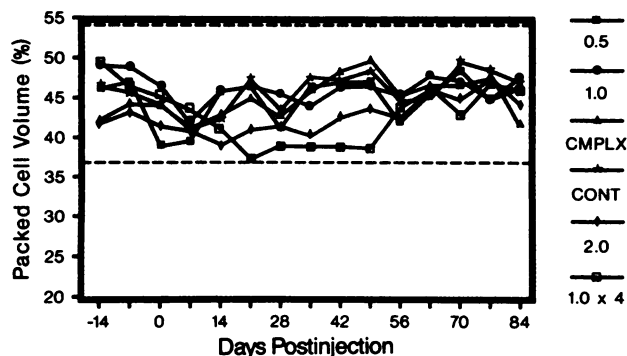


FIGURE 6
Mean packed cell volumes in groups of normal beagles given varying doses of ^{153}Sm -EDTMP as described in Figure 1.

humeral shafts was relatively hypoplastic at the beginning of the experiment in these mature animals. Since none of the peripheral blood sample tests gave any indication of preexisting marrow suppression at the onset of the experiment, the relative inactivity of the bone marrow in the long bones was considered to be normal. Following administration of the radioisotope to the non-control groups there seemed to be a slight drop in the activity of the marrow in these locations, but the severity of the suppression did not parallel that seen in the peripheral blood counts. Subjective microscopic evaluation of bone marrow samples taken at or near the end of the observation period indicated that the activity of the marrow in the long bones was generally increased over that observed in the baseline samples.

None of the other clinical pathologic parameters monitored indicated any apparent injury to the organ system which they represented. Values for these parameters did not ever fall outside the normal range used by our laboratory.

DISCUSSION

The study indicated significant alterations in the serum ALP levels in the absence of hepatocellular injury. While it is true that the liver's bile duct system is the most prolific source of this enzyme, the skeleton is its second most common site of origin. Therefore, it is reasonable to hypothesize that the skeleton, not the liver, is the source of this enzyme's elevation. Unfortunately, isoenzyme analysis for the skeletal form was not performed in this study.

It was presumed, from the outset, on the basis of previously reported work (5-7) that bone marrow was the normal tissue most likely to be severely damaged by intravenous administration of ^{153}Sm -EDTMP (1,2,12-14). The close physical proximity of the bone marrow to the target tissue (bone matrix) and the well established sensitivity of the proliferating marrow cells to ionizing radiation make these the cells most likely to suffer severe damage from beta particle radiation originating from the matrix of the cortical and trabecular bone. While there is a significant amount of energy release associated with the production of samarium's 28% abundant 103 keV gamma, much of this energy leaves the body due to the penetrating nature of this photon and the principal mode of damage is therefore associated with the beta particle.

Decreased numbers of platelets in the peripheral blood were consistently produced in all animals and the degree of depression in the platelet counts appeared to be dose related (Fig. 5). The animals which received the lowest doses of radiation also had the least degree of platelet depression. In some of the animals which received the 37 MBq/kg \times 4 and 74 MBq/kg dose levels of radiopharmaceutical, the platelet levels fell to ex-

tremely low levels, (<10% of the minimum normal value). However, none of these animals exhibited any of the expected clinical signs of decreased hemostasis capability of the blood. The dogs tolerated the minor surgical procedure of a bone marrow biopsy without excessive hemorrhage. Therefore, the decrease in the peripheral blood platelet counts induced by this agent did not produce clinically significant problems.

There were decreases in the number of all circulating WBC types. The timing and severity of the depression in the WBCs essentially paralleled that of the platelets; however, severe platelet depletion did not necessarily herald the same degree of decrease in the WBC count and vice versa. None of the animals showed any apparent signs of infection such as might be expected in an animal with severe leukocyte deficiency. While the WBC counts consistently dropped to abnormal levels in all animals, in the higher dose groups the severity of the drop did not always closely parallel that of other dogs in the same group. As would be expected, a more uniform response was evident in the high dose group animals (Fig. 7A-C).

The depletion of cells produced by the marrow extended to the red blood cells as well. The much longer half-life of the red blood cells apparently served to protect the animals from development of a severe anemia, however. The higher dose group animals did demonstrate mild decreases in the hematocrit several weeks after the injection of the radioisotope. This effect was most apparent in the multidose group. Such a reaction was to be expected due to the higher total dose and total time of exposure in this group. Although an apparent reduction in the packed cell volume is evident when the high dose group is compared to the other groups, the severity of the drop is relatively minimal (Fig. 6). The packed cell volume was not reduced below the normal range of variation for dogs.

Although the bone marrow response demonstrated that significant radiation dosage to the marrow was occurring, it also indicated that the marrow was apparently able to recover quickly from the effects of the dosage. Animals in the multidose group even appeared to be in the early stages of recovery prior to receiving the full radiation dose from the last injection.

There was concern that recovery would not occur because some human patients treated for metastatic bone neoplasia with ^{32}P developed permanent, fatal aplastic anemia (7). The situation with ^{32}P is different because phosphorous does not have the specificity for bone matrix that rare earth chelates have and is actively taken up by cells with high levels of DNA and RNA synthesis such as the marrow cells resulting in significant irradiation of marrow stem cells as well as the osteocytes. The high energy beta particle of ^{32}P ($E_{\beta_{\text{max}}} = 1.710 \text{ MeV}$) with its long mean range also results in further penetration of the beta particle through soft

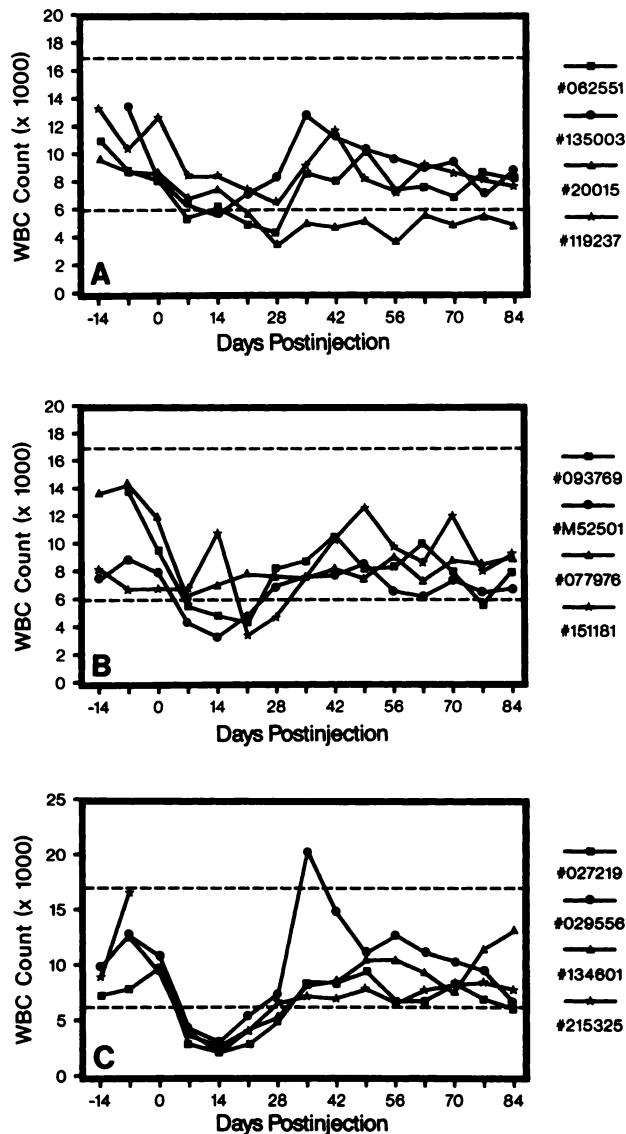


FIGURE 7
The white blood cell count response of individual animals in different dose groups: (A) 0.5 mCi (18.5 MBq)/kg, (B) 1.0 mCi (37 MBq)/kg, and (C) 2.0 mCi (74 MBq)/kg for ^{153}Sm -EDTMP. As the dose increases the response of the animals' cell counts becomes more uniform.

tissue from its source, producing a larger zone of radiation around the bone. The half-life (14.28 days) of this isotope also results in a protracted period of irradiation. All of these factors combine to increase the damage to the marrow cells. The medium energy beta particle ($E_{\beta_{\text{max}}} = 0.80 \text{ MeV}$) of ^{153}Sm with its shorter beta particle range and 46.8 hr (1.95 day) half-life may reduce the level of bone marrow damage. In this study the return of the marrow to normal activity, as indicated by the level of circulating cells, was rapid. This was true even when the given dose was twice the minimum estimated necessary to have a possible tumoricidal effect. Even when 37 MBq/kg was administered once weekly for

four consecutive weeks, the bone marrow was not permanently depressed. There appeared to be a stabilization in the number of circulating cells before the course of injections was completed in this group of animals (Figs. 4 and 5). These results would seem to indicate that the reduction in marrow produced cells was not logarithmically related to administered dose as is the case with homogenous mammalian cell culture lines when subjected to ionizing radiation (15). Therefore either there is a strong recovery and repair mechanism at work which minimizes injury to the bone marrow stem cells or the dose being received by these stem cells is less than expected.

Several reasons may be proposed for the apparent resiliency of the marrow in these animals. It is possible that the relatively short period of radiation to the marrow has less of an effect on the stem cells of the marrow population than does a more prolonged irradiation. Another explanation might be that in a healthy adult animal the active bone marrow is present in the ends of the long bones and in the flat bones of the axial skeleton. These are also the areas of greatest blood perfusion and bone remodeling, hence they are the regions which will have the greatest initial trapping of a bone seeking radioisotope. But as the initial damage to the marrow is manifest, there may be recruitment of the marrow stem cells in other sites that are not as intimately associated with the trabecular bone, i.e., the marrow in the shafts of the long bones. Since this marrow is somewhat physically removed from the radionuclide deposited with the cortical bone, it receives much less radiation than the marrow in the usual locations. Thus, the resistance of the marrow to injury may be dependent upon its physical location within the bone and not to an intrinsic insensitivity of the marrow cells. Such a mechanism seems to be supported by the apparent increase in bone marrow activity observed in the proximal femur of the animals in this study. It seems likely that both of these mechanisms may play a role in making the bone marrow cells resilient to the radiation effects of ^{153}Sm radioisotope EDTMP complex. Other, less obvious, mechanisms may also play a significant role.

Further evidence for the importance of this mechanism was reported by Appelbaum et al. (16). It was reported that iv administration of very high doses of ^{153}Sm -EDTMP (i.e., up to 1.11 GBq/kg) into beagle dogs produced only transient leukocyte and platelet suppression, indicating that the surviving marrow cells will efficiently repopulate the bone marrow and that extremely high doses of this radiopharmaceutical may be adequately tolerated, expanding its therapeutic potential.

The reason for the high incidence of cystitis is unclear, but may be related to the confinement in exercise runs for long periods of time. This restriction was

imposed by regulations pertaining to animals which have been administered radioactive materials. Such confinement would undoubtedly result in higher bacterial exposure rates and possibly in urine retention, both of which predispose animals to cystitis. Also, housing of animals in a veterinary hospital may result in increased exposure to pathogenic bacteria, even though the animals are housed in a ward separate from patients and other research animals. The cystitis was easily controlled as outlined above and did not result in any observed clinical problems for the animals.

SUMMARY

The recoverability of the bone marrow demonstrated in this series of experiments is encouraging for the further development of this agent and others like it as a treatment modality for both primary and metastatic skeletal neoplasias. This is especially encouraging when it is noted that a dose of 18.5 MBq/kg caused only minor depression of the white cell and platelet counts. This dose is sufficient to deliver a calculated absorbed dose of ~20 Gy, well within the range of total radiation doses normally used for palliation of bone pain due to osseous metastasis (5–40 Gy) (4). Further work needs to be done in animals to elucidate those variables which favor survival of the bone marrow stem cells so that they may be exploited by modification of the radioisotope, its carrier, or both, in an attempt to improve the lesion to non-lesion dose ratio. Reduction of the bone marrow effects would permit administration of higher doses of radioisotopes, thus improving control of the neoplastic disease.

The very minor alteration in vital organ functions, other than the bone marrow, detected in this study indicates that both the radiobiologic and chemical effects of the ^{153}Sm -EDTMP on these organs is minimal and would not be a limiting factor in the amount of the pharmaceutical given to a patient. The ability of the dogs to tolerate the radioisotope dosages used in this study suggests that this compound could be used to palliate metastatic bone neoplasia.

If improvements in the lesion to non-lesion ratio of radioisotope deposition can be achieved there is little reason why curative doses of radiation cannot be delivered to osseous neoplastic disease in some patients using agents of this type. Accomplishing this with an agent which causes little or no discomfort, inconvenience or danger to the patient would be a significant advance in the treatment of metastatic cancer.

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