EFFECTS OF INCREASING DOSES OF SAMARIUM-153-ETHYLENEDIAMINETETRAMETHYLENE PHOSPHONATE ON AXIAL AND APPENDICULAR SKELETAL GROWTH IN JUVENILE RABBITS

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Introduction:
Osteosarcoma often occurs in skeletally immature individuals. Previous studies have reported that \(^{153}\)Sm-EDTMP is an effective component of multi-modality therapy for treatment of primary bone tumors. Samarium-153-EDTMP is currently being investigated as a therapy for treatment of juvenile osteosarcoma. Upon injection, \(^{153}\)Sm-EDTMP localizes in areas of increased osteoblastic activity, including regions of bone growth and tumor formation and produces ionizing radiation through medium energy beta particle emission to a diameter of 2 mm. In immature bone, \(^{153}\)Sm-EDTMP localizes in the metaphyseal and epiphyseal regions of bone. However, due to the length of the beta particle emission, radiation damage to the growing physis cartilage may also occur. In previous investigations, the effects of a lower palliative dose of \(^{153}\)Sm-EDTMP on the development of long bone physis in juvenile rabbits were determined and correlated to radiographic and histologic physeal cartilage damage. In addition, a recent biodistribution study has allowed the quantification of radiation distribution in the bone and determination of the dose delivered to the physis from all tissues within the bone. However, comprehensive evaluations of the effects of \(^{153}\)Sm-EDTMP on bone growth have not been performed. In this study, we hypothesized that damage to the physis cartilage of juvenile rabbits secondary to metaphyseal and epiphyseal localization of the radiopharmaceutical would result in appendicular and axial skeletal growth impairment compared to placebo or vehicle-treated controls. The objectives of the study were to: 1) evaluate the late effects of \(^{153}\)Sm-EDTMP on skeletal structures during growth and 2) determine if there is a dose response to \(^{153}\)Sm-EDTMP with respect to growth of long bones.

Materials and Methods:
This experiment was conducted in compliance with the regulations of the Animal Care and Use Committee of the University of Missouri-Columbia. Eight-week-old female New Zealand White rabbits were divided into 3 treatment groups (n=6). Low dose (1 mCi/kg), medium dose (3 mCi/kg) and high dose (6 mCi/kg). Each rabbit was intravenously administered a pre-determined dose of \(^{153}\)Sm-EDTMP. Rabbits in the control group received a sham injection of saline. Physeal distribution of \(^{153}\)Sm-EDTMP was confirmed using nuclear scintigraphy and 2D digital autoradiography (Fig 1). The rabbits, radii and thoracolumbar spine of each rabbit were radiographed every two months until physical closure (10 months). Measurements were made of tibial, radial and vertebral bone length to assess for attenuated bone growth. Skeletal conformation was subjectively assessed radiographically and on physical examination for evidence of spinal curvature or angular limb deformities. A Kruskal-Wallis One-Way ANOVA on Ranks and a Dunn’s All Pairwise Multiple Comparison Procedure were performed to determine the differences in bone length among groups at the various time intervals with significance set at p<0.05.

Figure 1: A sectioned tibia (A) and representative digital autoradiogram (B) of \(^{153}\)Sm-EDTMP deposition in the tibia of an 8-week-old New Zealand White rabbit. A false color scale of radioactivity concentration is shown at right. Nuclear scintigram (C) showing the homogenous distribution of the radioactivity in the region of the physis. The sectioned tibia indicates the location of the epiphysis (E), physeal (P), metaphysis (M), marrow (RM) and diaphysis (D).

Discussion:
High dose \(^{153}\)Sm-EDTMP caused stunted growth of the tibia, radius and lumbar vertebrae in the two months following administration when compared to controls and medium and low dose groups. These data suggest that clinically significant bone shortening may occur as the result of high dosage administration of \(^{153}\)Sm-EDTMP as a result of damage to the physeal cartilage. The damage apparently occurred uniformly across the physis in rabbits, however, in that neither spinal curvature nor angular limb deformities resulted in this study. Because of the abbreviated period of longitudinal skeletal growth in this model and chosen radiographic sampling intervals, it remains difficult to determine if any degree of growth recovery occurred following the \(^{153}\)Sm-EDTMP –induced physeal insult. However, the effects on axial and appendicular bone growth have immediate clinical implication for the use of \(^{153}\)Sm-EDTMP in the treatment of osteosarcoma in children. Further investigation regarding the effects of bone seeking radiopharmaceuticals on bone growth and developing physeal cartilage is warranted.

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References:

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