UPTAKE OF [^{99m}Tc]TECHNETIUM METHYLENE DIPHOSPHONATE IN THE GROWTH PLATES OF THE RABBIT TIBIA DURING THE FINAL PART OF EPIPHYSEAL GROWTH ACTIVITY

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Uptake of ^{99m}Tc-MDP was measured in the proximal and distal growth plate of the rabbit tibia during the final phase of growth. Scintigraphic data were compared with roentgenographically measured tibial length and signs of bony fusion of the growth plates. Uptake by the proximal tibial growth plate was higher than in the distal tibial plate. Uptake decreased on cessation of growth and during subsequent bony fusion. In particular in the proximal tibial region, uptake was still high after cessation of longitudinal growth, which illustrates that during the final period of growth uptake of ^{99m}Tc-MDP by a roentgenographically still open growth plate does not necessarily indicate that such a growth plate still contributes to longitudinal growth. Decrease in uptake during the final phase of growth should be considered, when bone scanning is part of a research protocol.

Keywords : epiphysis ; growth plate ; technetium ; bone scintigraphy ; tibia.
Mots-clés : épiphyse ; cartilage de croissance ; technetium ; scintigraphie osseuse ; tibia.

INTRODUCTION

[^{99m}Tc]Technetium methylene diphosphonate (^{99m}Tc-MDP) is a widely used agent for bone scintigraphy. In growing long bones the target site for concentration of the isotope is the osteochondral junction in the epiphyseal growth plate which is the site of ossification and resorption (1, 2, 4).

Longitudinal growth, epiphyseal development, and bony fusion of growth plates are known to vary from bone to bone, between different epiphyses in the same bone and, on occasion, within the same epiphysis (5, 6). The final part of the growth period is controlled by largely unknown local and systemic mechanisms (6). Cessation of growth and subsequent closure of the epiphyseal growth plate are not well documented.

In previous studies we measured uptake of ^{99m}Tc-MDP in epiphyseal regions of the tibias of rabbits during distraction epiphysiolysis, near and after the end of growth (7, 8). In these experiments, uptake reached a maximum during the distraction phase and decreased in the weeks thereafter. This decrease was explained as indicative for progressive ossification, reduced metabolic activity and changes in vascularity. In the literature no data were available on uptake of ^{99m}Tc-MDP in the epiphyseal regions during the final part of growth. To validate our conclusions in these previous experiments we measured uptake of ^{99m}Tc-MDP in proximal and distal epiphyseal regions of the rabbit tibia from a few weeks before the end of the growth period until skeletal maturity was reached. Scintigraphic data were compared with roentgenographic length measurements on the tibia and with signs of bony fusion of the epiphyseal growth plates.

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METHODS

Animals

Five female New Zealand white rabbits (each weighing about 3.5 kg) were used in this study. At the start of the experiment the animals were 18 weeks old. At that age the tibia has reached at least 95% of its final length (5). At the end of the experiment the animals were 31 weeks old which is at least 2 weeks after reaching skeletal maturity (3, 5). The animals were housed individually in stainless steel cages in climate-controlled rooms and had free access to water and food.

Scintigraphy

The rabbits were injected intravenously with 175 MBq ^{99m}Tc-MDP. Two hours later, under general anesthesia, a scintigram was made using a gamma camera (Pho-gamma LFOV IV, equipped with a 140-keV LEAP collimator). With the detector facing upward, the rabbit was positioned in the field of view. Regions of interest of standard size and closely approximating the proximal and distal epiphyseal regions of the tibia were selected over the right and left legs (fig. 1). An additional region of interest was selected over the middle of the tibial shaft. The contribution from the tissue background radioactivity was negligible (fig. 1). The radioactivity in the regions of interest was measured. In each animal the uptake of radioactivity in the epiphyseal regions was divided by the uptake in the midtibial diaphysis of the corresponding leg (uptake ratio). Scintigrams were made weekly. The reproducibility of repeated measurements in any one animal was excellent. The variation in the midtibial region indicative of dose variation and measurement stability was 5-10%.

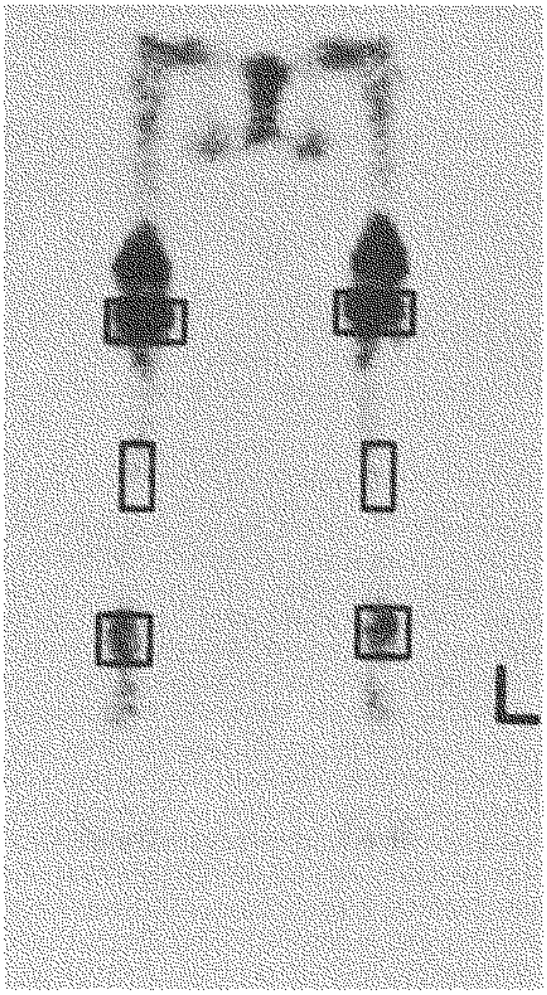

Fig. 1. — Scintigram of a rabbit's hind legs showing the selected regions of interest. L indicates the left leg. The tissue background radioactivity is negligible.

Roentgenography

Weekly, under general anesthesia, dorsoventral roentgenograms were made of both legs with the animal in prone position. Both legs were positioned parallel to each other in a removable plaster splint covering the ventral, medial and lateral side of the tibia and the distal two-thirds of the femur. Hip joints were extended as much as possible, knee joints were extended completely and ankle joints were maintained in maximal plantar flexion. The rotation of both legs was controlled by manually fixing both feet. A radio-opaque ruler was placed parallel to the longitudinal axis of both tibias to facilitate the measurement of length. Roentgenograms were made on a Philips M CD 125 roentgen apparatus with the collimator light centered at both knee joints. The tube was positioned over the animal platform at a distance of 1 m. The tibial length was defined as the distance between the most proximal edge of the proximal medial condyle and the most distal tip of the fused tibia-fibular complex (lateral malleolus), and was measured in mm directly on the roentgenograms. Length is expressed relative to the maximum length at the end of growth at 30 weeks of age. Differences between length at a certain age and maximum length at 30 weeks were statistically evaluated using the Student's *t*-test.

RESULTS

The weekly uptake ratios of ^{99m}Tc-MDP measured over proximal and distal epiphyseal regions of the tibia are presented in fig. 2. The uptake ratios were similar in the right and left legs, and they decreased in time. Uptake was higher in the proximal than in the distal region. The uptake ratio in the distal tibia leveled off around 27 weeks, in the proximal tibia around 29 weeks.

The tibial length increased during this period of growth (fig. 3). At 24 weeks of age the tibial length was not significantly different from the length at a later age, indicating that at 24 weeks

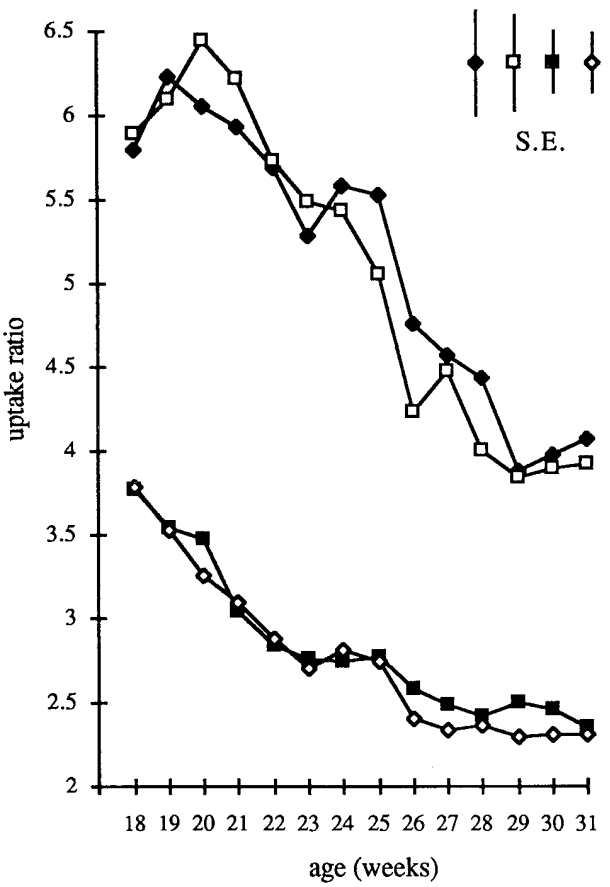

Fig. 2. — Uptake ratio of ^{99m}Tc-MDP measured over the proximal (upper curves) and distal (lower curves) epiphyseal regions of the tibia. Open symbols represent the right tibia and closed symbols the left tibia. The means of measurements on 5 animals are presented. The standard errors per set of data points constituting a curve were so similar that, for clarity of presentation, pooled standard errors are indicated.

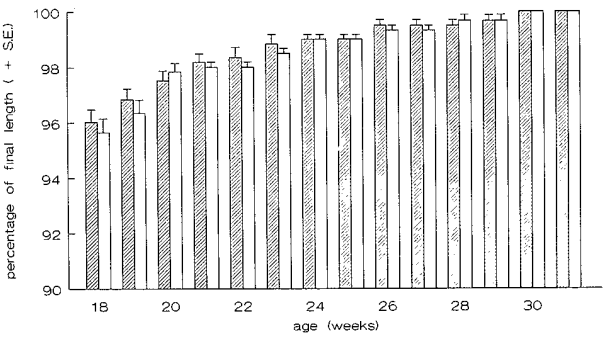

Fig. 3. — Tibial length measured on roentgenograms. The open bars represent the right tibia, the hatched bars the left tibia. The means of measurements on 5 animals are presented. Length is expressed relative to the maximum length at 30 weeks. Differences between length at a certain age and maximum length at 30 weeks were statistically evaluated using Student's t-test. After 24 weeks the length did not increase significantly. At 18-23 weeks the length was significantly less than maximal ($p < 0.001$ at 18-19 weeks; $p < 0.01$ at 20-21 weeks, and $p < 0.05$ at 22-23 weeks).

the end of longitudinal growth had been reached. The mean length of both left and right tibias was 12.0 ± 0.2 cm at 30 weeks.

On roentgenograms the distal tibial growth plates were already obliterating at the start of the experiment and disappeared almost completely at week 27. The proximal tibial and proximal fibular growth plates closed between 28 and 30 weeks.

DISCUSSION

In spite of the complexity of factors contributing to the growth and bony fusion of the growth plates, in all animals extent, rate, and pattern of uptake of ^{99m}Tc-MDP in proximal and distal epiphyseal tibial regions were symmetrical with regard to left and right limbs (fig. 2).

The higher uptake of ^{99m}Tc-MDP in the proximal tibial region in comparison with the distal region (fig. 2) may be caused by several factors. The higher uptake of the bone-seeking agent may reflect the higher rate of growth reported for the proximal tibia (9). In addition, the proximal tibial growth plate represents a larger area of uptake than the distal tibia, and the extent of uptake is proportional to the area available for absorption (1). Additional uptake from the growth plate

of the proximal fibula which has a similar rate of growth and time of fusion to the proximal tibial growth plate (8), was also included in the proximal tibial measurements.

The tibial length measurements (fig. 3) correspond well with data reported by others (3, 5). Because bony fusion of the distal tibial growth plate sets in at 16 weeks of age (6), in this experiment tibial growth in length was probably determined by the proximal growth plate only. In the period of epiphyseal growth activity till the age of 23-24 weeks, while the rate of tibial growth decreased, the area of uptake of the proximal epiphyseal growth plate decreased due to the diminishing physeal function, resulting in a decreased uptake of the radionuclide. After cessation of growth, bony fusion of the proximal tibial growth plate started and proceeded until the age of 29 weeks which is the ultimate age of closure (5, 6). In the process of bony fusion the area of uptake decreases, which is reflected by a further decrease in uptake of ^{99m}Tc-MDP.

Bony fusion at the distal epiphyseal region of the tibia with a concomitant decrease in uptake of ^{99m}Tc-MDP continued until 27 weeks which is the ultimate age of closure of the distal growth plate (5, 6).

The decrease in uptake in the proximal tibia throughout the observation period depends upon cessation of growth and the subsequent process of bony fusion, while in the distal tibia bony fusion is the only factor.

This study illustrates that during the final part of epiphyseal growth activity the level of uptake of ^{99m}Tc-MDP depends on the location and stage of development of the growth plates involved. This must be taken into account if bone scanning is part of a research protocol. In our previous studies (7, 8), any change in uptake due to factors related to distraction epiphysiolysis will have been superimposed upon the effect of natural decrease in uptake after cessation of growth shown in the present study. The data also illustrate that uptake of ^{99m}Tc-MDP by an epiphyseal growth plate which is roentgenographically still open, should not necessarily be interpreted as an indication that the growth plate still contributes to longitudinal growth.

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SAMENVATTING

P. M. VAN ROERMUND, C. HAARING, P. P. VAN RIJK, W. RENOOIJ. Uptake of [^{99m}Tc]technetium methylene diphosphonate in the growth plates of the rabbit tibia during the final part of epiphyseal growth activity.

De opname van ^{99m}Tc-MDP in de proximale en distale groeischijf van de tibia van het konijn werd gemeten tijdens de laatste fase van de groei. De scintigrafische gegevens werden gecorreleerd aan lengtemetingen van de tibiae en tekenen van verbening van de groeischijven, verkregen van roentgenfoto's. De opname van ^{99m}Tc-MDP door de proximale groeischijf was groter dan

in de distale groeischijf. De opname werd minder tegen het einde van de groei en de hieropvolgende fase van verbening. In het bijzonder in het proximale deel van de tibia bleef de opname hoog na het stoppen van de lengte-groei. Dit laatste illustreert dat de opname van ^{99m}Tc-MDP door een groeischijf die in de laatste fase van de groei op de roentgenfoto nog open is, niet noodzakelijkerwijze er op wijst dat deze groeischijf nog bijdraagt aan de lengte-groei. Men moet bedacht zijn op deze vermindering van opname van ^{99m}Tc-MDP in de laatste fase van de lengte-groei, zeker indien bot-scintigrafie deel uitmaakt van een wetenschappelijk onderzoeksprotocol.

RÉSUMÉ

P. M. VAN ROERMUND, C. HAARING, P. P. VAN RIJK, W. RENOOIJ. Captation du diphosphonate de méthylène au (99m Tc)technetium dans le cartilage de croissance du lapin au cours de la phase finale de la croissance épiphysaire.

La captation de DPM 99mTc dans le cartilage de croissance proximal et distal du tibia, chez le lapin, fut mesurée pendant la dernière phase de la période de croissance. Les données scintigraphiques furent corrélées à la croissance en longueur du tibia et aux signes radiologiques d'ossification du cartilage. La captation de DPM 99mTc dans le cartilage proximal était supérieure à la captation dans le cartilage distal. La captation diminua en fin de croissance et pendant la phase d'ossification ultérieure. Dans la partie proximale du tibia la captation resta élevée après la fin de la croissance en longueur. Ceci illustre que la captation du DPM 99mTc par un cartilage de croissance qui est encore radiologiquement ouvert au cours de la dernière phase de la croissance, n'indique pas nécessairement que ce cartilage contribue encore à l'allongement de l'os. Il faut être conscient de cette diminution de captation du DPM 99Tc au cours de la dernière phase de la croissance, surtout lorsque la scintigraphie osseuse est intégrée dans un protocole d'étude scientifique.