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Modeling the time dependent biodistribution of Samarium-153 ethylenediamine tetramethylene phosphonate using compartmental analysis

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ABSTRACT

Aim: The main purpose of this work was to develop a pharmacokinetic model for the bone pain palliation agent Samarium-153 ethylenediamine tetramethylene phosphonate ([153Sm]-EDTMP) in normal rats to analyze the behavior of the complex.

Background: The use of compartmental analysis allows a mathematical separation of tissues and organs to determine the concentration of activity in each fraction of interest. Biodistribution studies are expensive and difficult to carry out in humans, but such data can be obtained easily in rodents.

Materials and methods: We have developed a physiologically based pharmacokinetic model for scaling up activity concentration in each organ versus time. The mathematical model uses physiological parameters including organ volumes, blood flow rates, and vascular permabilities; the compartments (organs) are connected anatomically. This allows the use of scale-up techniques to predict new complex distribution in humans in each organ.

Results: The concentration of the radiopharmaceutical in various organs was measured at different times. The temporal behavior of biodistribution of 153Sm-EDTMP was modeled and drawn as a function of time.

Conclusions: The variation of pharmaceutical concentration in all organs is described with summation of 6–10 exponential terms and it approximates our experimental data with precision better than 2%.

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1. Background

According to the principles of humane experimental technique, the use of other researchers' data has been one of the mainly recommended actions allowing the 3Rs concepts to reduce the number of experimental procedures involving animal and improve results.[1] In the same way, compartmental analyses support the radiopharmaceuticals design permitting a mathematical separation of tissues and organs to determinate the concentration of activity in each fraction of interest and pointing toward inconsistency in biodistribution and dosimetry studies. Additionally, by compartmental analysis it is possible to consider different chemical species and to predict metabolites.[2]

Mathematical models that describe the kinetic processes of a particular agent may be used to predict its behavior in regions where direct measurements are not possible but where sufficient independent knowledge about the physiology of the region is available to specify its interrelationship with the regions or tissues in which uptake and retention can be measured directly. These models can account for the presence of metabolic products.[3–6] Compartmental modeling is the most commonly used method for describing the uptake and clearance of radioactive tracers in tissue.[7–9] These models specify that all molecules of tracer delivered to the system (i.e., injected) will at any given time exist in one of many compartments. Each compartment defines one possible state of the tracer, specifically its physical location (for example, intravascular space, extracellular space, intracellular space, synapse) and its chemical state (i.e., its current metabolic form or its binding state to different tissue elements, such as plasma proteins, receptors). Often, a single compartment represents a number of these states lumped together. Compartments are typically numbered for mathematical notation.[10]

The compartmental model also describes the possible transformations that can occur to the tracer, allowing it to move between compartments. The model defines the fraction or proportion of tracer molecules that will move to a different compartment within a specified time. This fractional rate of change of the tracer concentration in one compartment is called a rate constant and has units of inverse time.[10]

The physiological interpretation of the source and destination compartments defines the meaning of the rate constants for movement of tracer between them. For a freely diffusible inert tracer, the rate constant of transfer from arterial blood to the tissue compartment will define local blood flow. By determining these rate constants (or some algebraic combination of them), quantitative estimates or indices of local physiological parameters can be obtained. The underlying goal of all modeling methods is the estimation of one or more of these rate constants from tissue radioactivity measurements.[2,10]

In this study, the compartmental analyses were used to generate a time-dependence model of biodistribution of [^{153}Sm]-EDTMP, an agent for bone palliation radiotherapy. Chemotherapy or hormonal therapy may be used for both soft tissue and bone metastases and can be effective until the disease becomes refractory to these agents. External beam radiotherapy provides effective pain control with short courses of high dose per fraction and a low toxicity, if the metastatic disease is not extensive; however, the toxicity rapidly increases with wide radiation fields.[11]

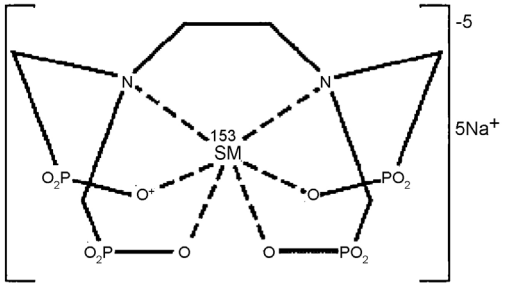

Fig. 1 – Chemical structure of [^{153}Sm]-EDTMP.

Systemic therapy with radionuclides linked to bone seeking agents is a treatment option for patients with disseminated skeletal metastases, owing to its efficacy, low cost and low toxicity.[12] Radionuclides suitable for systemic metabolic radiotherapy of bone pain include Phosphorous-32 (P-32), Strontium-89 (Sr-89), Rhenium-186 (Re-186) chelated with hydroxyethylidene diphosphonate (HEDP) and Samariumm-153 (Sm-153) chelated with ethylenediamine tetramethylene phosphonate (EDTMP).[13–16]

Considerable bone marrow suppression due to the presence of higher energy β particles is a major constraint toward a widespread use of P-32 (mean $\beta = 695$ keV, $t_{1/2} = 14.3$ days) and Sr-89 (mean $\beta = 583$ keV, $t_{1/2} = 50.5$ days). Apart from that, the absence of imageable γ photons and long half life (especially in case of Sr-89) are often cited as drawbacks. Beta emitters with short half-lives, like Re-186 (mean $\beta = 362$ keV, $\gamma = 137$ keV, $t_{1/2} = 3.7$ days) and Sm-153 (mean $\beta = 233$ keV, $\gamma = 103$ keV, $t_{1/2} = 1.9$ days), deliver their radiation dose at higher dose rates, which may be therapeutically more effective than equivalent doses given at lower dose rates. The short range of beta emission of these radionuclides may be of advantage in limiting red marrow irradiation.[17] Beside beta ray, ^{153}Sm emits gamma radiation and conversion electrons with 103 keV and 55 keV energies, respectively. Gamma ray at this energy range makes nuclear imaging feasible, while the process of radiotherapy is carried out. Finally, ^{153}Sm decays to stable nuclide ^{153}Eu.[18,19] ^{153}Sm-ethylenediamine tetramethylene phosphonic acid ([^{153}Sm]-EDTMP) (Fig. 1) localizes in the skeleton by chemo-absorption of the tetraphosphonate by hydroxyapatite and by the formation of Samarium oxide involving oxygen on the hydroxyapatite molecule. Early phase I/II studies were published more than ten years ago and since then, this agent has been clinically used worldwide for pain palliation in symptomatic bone metastases from several cancers, mainly prostate and breast.[20–22]

Mathematical biodistribution models are an alternative approach to the direct calculation of cumulated activity in the field of radiopharmaceuticals dosimetry. Often, it is impractical to measure the time–activity curves of all the source regions. When the physiological interactions of these regions with the blood or with other directly measurable tissues are known, the time–activity curves of unmeasured tissues can be inferred by these models. Biodistribution modeling can also be used to separate the activities in the regions that overlap