Sr-89 therapy: Strontium kinetics in disseminated carcinoma of the prostate

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Abstract. Strontium kinetics were investigated in a group of 14 patients receiving 89Sr palliation for metastatic bone disease secondary to prostatic carcinoma. Using 85Sr as a tracer, total body strontium retention \( R(t) \) was monitored for a 3 month period following 89Sr administration, and at 90 days was found to vary from 11% to 88% and to correlate closely with the fraction of the skeleton showing scintigraphic evidence of osteoblastic metastatic involvement. Strontium renal plasma clearance varied from 1.6 \( 1/\text{day} \) to 11.6 \( 1/\text{day} \), and in nine patients was significantly reduced compared with values found in healthy adult men, probably due to increased renal tubular reabsorption associated with the disturbance of calcium homeostasis. Renal clearance rate was the principal factor determining \( R(t) \) for \( t < 6 \) days, and was an important secondary factor at later times. Over the interval 30 days < \( t < 90 \) days, \( R(t) \) was closely fitted by the power law function \( R(t) = R_{30} (t/30)^{-b} \), with \( R_{30} \) and \( b \) showing the close correlation expected from the effect of \( R(t) \) on strontium recycling. The correction of the data for this effect to determine the true skeletal release rate is described. Measurement of localized strontium turnover in individual metastatic deposits from whole body profiles and scintigraphic images gave retention curves that typically rose to a plateau by 10 days after therapy, and then decreased very slowly. In contrast, retention curves for adjacent normal trabecular bone showed more rapid turnover, peaking at 1 day and subsequently decreasing following a \( t^{-0.2} \) power law function. The changes in strontium kinetics found in metastatic bone disease are favourable to the objectives of 89Sr therapy.

Key words: 89Sr therapy – Prostatic carcinoma – Strontium kinetics – Metastatic bone disease

Pecher (1942) was the first to report a possible therapeutic role for the beta emitting radionuclide 89Sr in the palliation of bone pain associated with metastatic bone disease. Recently, interest in radiostrontium treatment was revived by Firusian et al. (1976) and Robinson (1986), and a multicentre clinical trial evaluating 89Sr therapy is at present in progress in the USA and UK. Patients participating in this trial and attending the Department of Nuclear Medicine, Southampton General Hospital, were also asked to take part in a study of strontium metabolism designed to improve knowledge of strontium kinetics in metastatic bone disease and permit estimates of absorbed dose to bone metastases and red bone marrow. In this report we present our findings for strontium kinetics in 14 patients with metastasising prostatic carcinoma, and discuss the ways in which metastatic bone disease modifies normal strontium metabolism. Our clinical findings following 89Sr therapy in these patients have been reported previously (McEwan et al. 1986).

Patients and methods

Patients

Strontium kinetics were investigated in 14 patients referred from an oncology clinic for 89Sr palliation of metastatic bone disease. The group all had histologically proven carcinoma of the prostate, and all had bone metastases demonstrated by skeletal radiography and 99mTc-MDP bone scintigraphy. They were referred for 89Sr having exhausted conventional treatment that included hormonal and cytotoxic therapies and localized radiotherapy, and provided their estimated survival exceeded 3 months. All gave informed consent to a clinical trial of 89Sr therapy, of which the present study formed part.

Administration of radiostrontium

Patients received a therapeutic dose of 89Sr together with a tracer dose of 85Sr for the kinetic study. Details of the emissions, half-lives and specific activities of the two radioisotopes are given in Table 1. Photon emission from 89Sr is limited to bremsstrahlung and a low abundance gamma emission at 910 keV, and the addition of 85Sr permitted a more comprehensive study of strontium metabolism than would otherwise have been possible. The first three patients received an 89Sr dose of 1.48 MBq/kg body weight and 40 MBq of 85Sr. Subsequent patients received 2.22 MBq/kg of 89Sr and between 10 MBq and 40 MBq of 85Sr. After measurement in an isotope assay calibrator, 89Sr and 85Sr were administered simultaneously via a peripheral vein over 1 min at a constant infusion rate. No adverse reactions were observed.

Plasma curves

Following injection of the patient, blood samples were drawn from a different vein at 5 min, 15 min and 30 min,
As part of the clinical evaluation of variations in WBM sensitivity were made by running a standard, all patient counts were normalized to the 30 min after injection, then daily during the first week, on 3 days during the second week, weekly up to 6 weeks and then every 2 weeks up to 3 months. Corrections for radioactive decay and small variations in WBM sensitivity were made by running a standard 10 kg phantom containing around 4 MBq of $^{85}$Sr through the WBM before every patient counting session. After subtraction of background and correction to the standard, all patient counts were normalized to the 30 min count to give percentage whole body strontium retention. The correction for $^{89}$Sr bremsstrahlung was found to be negligible. A print out of counts in 1 cm intervals for each whole body profile was kept for later analysis of strontium retention in selected regions of interest.

$^{85}$Sr scintigraphy

Towards the end of the study a high energy gamma camera collimator, rated to 511 keV and suitable for imaging $^{85}$Sr, became available, and was used to study strontium retention in selected small metastases and adjacent normal bone in each of the final six patients. Corrections for radioactive decay and variations in WBM sensitivity were made using scintiscan images of the WBM phantom. Anterior and posterior images were combined with emission measurements using a point source of $^{55}$Sr of known activity to determine uptake figures corrected for attenuation by overlying tissue using the technique described by Sudell et al. (1985).

$^{99m}$Tc MDP scintigraphy

As part of the clinical evaluation of $^{99m}$Sr therapy, all patients had whole body $^{99m}$Tc-MDP bone scintigraphy performed during the week preceding treatment. In order to provide a quantitative index of the extent of osteoblastic metastatic involvement for comparison with the strontium kinetics, the scintiscan images of every patient were analyzed as follows. The skeleton was divided into four anatomical regions: (i) spine, (ii) pelvis, (iii) shoulder girdle and ribs, and (iv) extremities, and each region was scored visually on a scale 0 to 10 on the apparent proportion of bone involved. The scores for each region of a patient's scan were then summed, and the sum renormalized on a scale 0 to 100 to give a measure of the total extent of skeletal involvement. We shall refer to this as the bone scan index (BSI).

Normal strontium kinetics

In view of the considerable literature on strontium metabolism in healthy individuals (Bishop et al. 1960; Cohn et al. 1962; Harrison and Sutton 1967; Likhtarev et al. 1975; Tothill et al. 1983), we did not feel justified in studying our own series of normal controls. The early studies of strontium kinetics were reviewed by Marshall et al. (1973), who adopted a mathematical model of alkaline earth metabolism which remains the basic of current schemes of bone dosimetry (ICRP, 1979). In this model the fractional total body retention $R(t)$ takes the form:

$$R(t) = (1 - p)e^{-mt} + p(1 + t/e)^{-b}$$

where $t$ is time measured in days. For strontium retention in a healthy individual, Marshall et al. adopted the following normal values: $p = 0.60$, $m = 0.25$, $e = 0.20$ and $b = 0.18$. Equation 1 has been simplified by omitting an exponential term due to bone resorption which is negligible on the time scale considered here.

Plasma strontium $P(t)$, expressed as the fraction of injected dose in the total plasma volume, is found by differentiating equation 1:

$$P(t) = V_{pl}k^{-1} \left| \frac{dR}{dt} \right|$$

$$= V_{pl}k^{-1} \frac{m(1-p)e^{-mt} + pb(1 + t/e)^{-b+1}}{e}$$

Table 1. Comparison of the physical properties and specific activities of $^{85}$Sr and $^{89}$Sr. A weak gamma emission at 910 keV arises from the decay of $^{89}$Sr to $^{89m}$Y with a branching ratio of $1 \times 10^{-4}$. Radioactive strontium was administered as the chloride.

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<th>$^{85}$Sr</th>
<th>$^{89}$Sr</th>
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<tbody>
<tr>
<td>Transition</td>
<td>Beta minus</td>
<td>Electron capture</td>
</tr>
<tr>
<td>(E_{max} = 1.46 MeV)</td>
<td>(910 keV)</td>
<td>514 keV</td>
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<tr>
<td>Gamma emission</td>
<td>50.5 days</td>
<td>64.8 days</td>
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<td>Specific activity</td>
<td>5 GBq/g</td>
<td>500 GBq/g</td>
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