Rhenium-188 sulphur colloid as a radiation synovectomy agent

Shyh-den Wang 1,4, Wan-Yu Lin 1, Bor-Tsung Hsieh 2, Lie-Hang Shen 2, Zei-Tsan Tsai 2, Gann Ting 2, Furn E Knapp Jr. 3

1 Department of Nuclear Medicine, Taichung Veterans General Hospital, No. 160, Sec. 3, Taichung Harbor Road, Taichung 407, Taiwan
2 Institute of Nuclear Energy Research, Taiwan
3 Oak Ridge National Laboratory, Tenn., USA
4 National Yang-Ming Medical College Taipei, Taiwan

Received 25 January and in revised form 12 February 1995

Abstract. Radiation synovectomy has been shown to be an effective treatment for the rheumatoid arthritic knee. In this study, we evaluated the suitability of rhenium-188 as a radiation synovectomy agent. In addition, we were successful in labelling sulphur colloid with 188Re. In vitro stability tests revealed that more than 95% of the 188Re remained in colloid form over a 3-day period. Intra-articular injection of 188Re sulphur colloid into arthritic rabbit joints was followed by gamma camera imaging to quantify the leakage. The mean retention percentages of 188Re colloid in arthritic knees were 93.7% (+1.4%), 90.8% (+1.7%) and 87.2% (+0.6%) at 1 h, 1 day and 2 days, respectively. A biodistribution study of the arthritic rabbits revealed that the highest activity outside the knees was in the liver and the kidneys. Our preliminary results indicate that 188Re sulphur colloid may be an effective radiopharmaceutical for radiation synovectomy.

Key words: Radiation synovectomy - Rhenium-188 colloid - Rheumatoid arthritis


Introduction

Radiation synovectomy has been developed as an alternative to surgical synovectomy. This procedure consists in an intra-articular injection of beta-emitting radiopharmaceuticals to counteract and control synovial inflammation. It is most often applied in the treatment of rheumatoid arthritis [1-4]. Many isotopes have been tested for their potential as synovial ablative agents. Phosphorus-32 and yttrium-90 are the two isotopes that have been most widely used for radiation synovectomy in the past [1-6]. However, these isotopes do not emit imageable gamma rays; thus quantitative dosimetric and leakage information is difficult to obtain from gamma camera imaging.

Rhenium-188 is carrier-free and available from an in-house generator system similar to the current technetium-99m generator. It is suitable for treatment of the knee owing to its deep tissue penetration (maximum: 11 mm; average: 3.8 mm). 188Re can be obtained from a 188W/188Re generator, which makes it suitable for clinical use. Gamma emission with an energy of 155 keV allows for the evaluation of leakage of radioisotopes and calculation of dosimetry by gamma camera imaging. In 1990, Venkatesan et al. developed a preparation of 188Re colloid for use in radiation synovectomy [7]. Their results were encouraging. In this study, we labelled sulphur colloid with 188Re and analysed the biodistribution following intra-articular injection in rabbits with antigen-induced arthritis to assess its applicability for radiation synovectomy.

Materials and methods

185Re production. 188Re was obtained from an alumina-based 188W/188Re generator, with the 188W supplied by the Oak Ridge National Laboratory (Tenn., USA). The 188W was produced by double-neutron capture of 186W. Elution with normal saline provided solutions of carrier-free 188Re sodium perrhenate (NaReO4) from the 188W/188Re generator [8-10]. High-performance liquid chromatographic analysis revealed that the 188Re eluate was >99% perrhenate. 188W/188Re generators have demonstrated consistently high 188Re yields and low parent breakthrough for periods of at least 2 months.

Production of 188Re colloid. The method of preparation of 188Re colloid was a modification of that reported by Venkatesan et al. [7], in which 188Re colloid was formed by acid reduction of sodium thiosulphate in the presence of perrhenate. In this study, we developed a new 188Re sulphur colloid kit. Each vial of sulphur colloid kit contains 40 mg sodium thiosulphate, 4.8 mg EDTA and 0.8 mg potassium perrhenate. Vials were reconstituted as required and radiolabelled by the addition of 1-2 ml of eluted sodium perrhenate solution. The optimal conditions were a reaction of 30 min at 95° C and pH=1. To ensure uniformity of the suspension, the
colloid was shaken for 5 min prior to administration. The particle size distributions were determined using a laser diffraction particle size analyser (Microtrac, FRA 9200, Leed & Northrup, USA).

In vitro stability test. Aliquots of 188Re colloid were added to tubes containing 10 ml of normal saline, phosphate-buffered saline (pH 7) and fetal calf serum. The tubes were stoppered and mixed continuously on a rotator. At intervals of 5 h, 1 day, 2 days and 3 days, the tubes were removed and centrifuged at 500 g for 5 min. Aliquots of the supernatants were counted using a gamma counter and the colloidal suspensions were readjusted to their original volumes and returned to the rotator. All counts were corrected for radioactive decay and expressed as a percentage of the total radioactivity at the beginning of the experiment.

Animal models. Twelve male mature New Zealand white rabbits, weighing 3 kg, were used in an antigen-induced arthritis model [6, 11]. The animals were sensitized intradermally with 1 mg ovalbumin solution (Sigma Chemical Co., St. Louis, Mo., USA), emulsified in an equal volume of Freund's complete adjuvant (Sigma Chemical Co., St. Louis, Mo., USA) and distributed over five sites on the back. The rabbits were resensitized 3 weeks after the second immunization. The rabbit knees were injected with 37 MBq 188Re colloid 2 weeks after injection of ovalbumin.

Imaging. Four rabbits were imaged using an Elscint ECT 609 gamma camera fitted with an APC 5R (medium-energy, medium-resolution) collimator. A 10% window was centered around 155 keV. The camera was positioned above the rabbit. The images were collected over a period of 5 min. They were recovered 1 h, 24 h and 48 h after injection. Regions of interest were set around the knee, with a background area outside the body of the rabbit. The results were calculated as the percent injected dose (% ID) retained in the knee over time.

Biodistribution. To determine the biodistribution of 188Re colloid the animals were slaughtered 24 h and 48 h after intra-articular injection (four rabbits at a given time). Samples of different organs were weighed and counted in a well-type gamma counter (Packard Cobra II, USA) to calculate resident activity in different organs.

Results

The radiochemical yield of 188Re colloid, obtained by thiosulphate acid reduction, was in the range of 90%. Particle sizing indicated that 6.8% of the particles were 10 μm or larger, 10.7% were 5–10 μm, 65% were 1–5 μm and 17.5% were 0.15–1 μm. In vitro stability tests (in normal saline, phosphate buffer pH 7, fetal calf serum) revealed that more than 95% of the 188Re activity remained in colloid form over a 3-day period. The mean retention percentages of radioactivity in arthritic knees, determined using a gamma camera, were 93.7%±1.4%, 90.8%±1.7% and 87.2%±0.6% at 1 h, 24 h and 48 h, respectively.

The results of the biodistribution study, expressed as % injected activity per gram of tissue, are summarized in Table 1. The highest activity outside the knees was found in the liver and the kidneys. The resident activities in the liver were 1.58% at 1 day and 1.45% at 2 days. The activities in the kidneys were 0.2% at 24 h and 0.04% at 48 h.

Discussion

Radioisotopes have been employed in the treatment of inflammatory arthritides for more than 40 years. However, they are not widely used owing to (a) the unacceptably high level of radiation delivered to non-target organs from leakage of radioactive material from the treated joints [12], (b) lack of availability and (c) high cost. Radioactive leakage from the inflamed joint can be reduced by means of three methods [13]. First, leakage can be reduced by using radioactive particles of optimum size: particles in the range of 2–5 μm are the most suitable [14]. Second, immobilization of the treated joints has been shown to reduce particle leakage [15]. Third, choosing an isotope with a short half-life minimizes the cumulative radiation dose. The use of a 188W/188Re generator system is cost-effective, as generators have long shelf-lives, resulting in a lower cost per dose. The use of generators may also increase the availability of radioisotopes for radiation synovectomy.

90Y colloid has been shown to be effective for the treatment of rheumatoid arthritis [16, 17]. 188Re colloid has similar beta energy characteristics to 90Y; however, its physical half-life is shorter than that of 90Y, which can effectively reduce the systemic radiation due to leakage from joints. In addition, the 155-keV gamma rays emitted from 188Re can be utilized to monitor extra-articular leakage and biodistribution of 188Re colloid.

Venkatesan et al. developed a preparation of 186Re colloid for use in radiation synovectomy [7]. However, the formulation of this radiopharmaceutical is prohibitively labour intensive [1]. Using our new method of

Table 1. Biodistribution of intra-articular injection of 188Re colloid in rabbits with induced synovitis

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>% injected activity per gram of tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lymph node</td>
</tr>
<tr>
<td>24</td>
<td>0.0016</td>
</tr>
<tr>
<td>48</td>
<td>0.0002</td>
</tr>
</tbody>
</table>