Holmium-166: a Potential Lanthanide Element in Radiotherapy*

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In the lanthanide series, the radionuclides ^{165}Dy and ^{169}Er have been used in synoviotherapy [1, 2]. Holmium-166 is also a lanthanide element which has nuclear characteristics suitable for therapeutic purposes. A neutron irradiation planning was developed in order to optimize the irradiation conditions for maximum values of specific activity and minimum radionuclidic contamination. In synoviotherapy the radioactive preparations are injected in a colloidal form. Therefore we developed the preparation of ^{166}Ho as a citrate colloidal solution. The radiation absorbed dose was calculated for the knee and the whole body and compared with the radiation absorbed dose due to ^{165}Dy and ^{169}Er for the same activity.

Neutron Irradiation Planning

Holmium-166 is produced by neutron irradiation of natural holmium: ^{165}Ho(n,γ)^{166}Ho. The main contaminant is ^{167}Ho which is produced by a double neutron capture side reaction. Using the computer code ISOTOP based on the Runge–Kutta algorithm [3] and according to the nuclear data for the holmium nuclides [4–6], we estimated the activities of the radionuclides involved in order to find a suitable irradiation scheme for different neutron fluxes and reactor spectra. The Westcott formalism [7] was used for the effective neutron capture cross-section calculation. Calculations were made assuming the following conditions: (i) sample weight (natural holmium) = 1 g; (ii) maximum irradiation time = 48 h; (iii) thermal neutron fluxes Φ (neutrons/cm^2 s) = 10^{12}, 10^{13}, 10^{14}; (iv) epithermal neutron index (Westcott formalism): $0 \leqslant r \leqslant 0.05$. Table I shows the calculated values of the specific activity, SA_0, and the radionuclidic contamination, RC_0, as a function of the irradiation time, t_i, for $\Phi = 10^{13}$ neutrons/cm^2 s, the epithermal neutron index being zero, *i.e.*, $r = 0$. The calculation has shown that for $\Phi \leqslant 10^{14}$ neutrons/cm^2 s and $t_i \leqslant 48$ h, the values of SA and RC are proportional to Φ. Even in the extreme conditions studied, the value of RC_0 is less than 0.13%. The value of the neutron capture resonance integral, I, of ^{165}Ho is high compared with the thermal neutron capture cross-section, σ_0: $I = 10.6\ \sigma_0$. This means that the contribution of epithermal neutrons to the growth of ^{166}Ho is significant. The dependence of the specific activity on the epithermal neutron index was found to be: $SA(r) = SA(r = 0) \times (1 + 11.3r)$. Let us assume that a sample of natural holmium of mass w g is irradiated during a time interval t_i at a position in a nuclear reactor where the thermal neutron flux is Φ and the epithermal neutron index is r, and suppose that one whishes to determine the ^{166}Ho activity after a decay time t_d. The desired quantity is

$$A(\Phi, t_i, r, t_d) = w \times SA_0 \times \frac{\Phi}{10^{13}} \times (1 + 11.3r) \times \exp(-0.0259 t_d) \times K$$

where SA_0 can be obtained from Table I, t_d is expressed in hours, and K is the neutron flux perturbation factor [8, 9]. The K value depends on the sample nature, geometry and dimension, and can be significant for holmium samples, because the neutron cross-section is relatively high.

TABLE I. Holmium-166 Specific Activity and Radionuclidic Contamination as a Function of the Irradiation Time for Thermal Neutron Flux $\Phi = 10^{13}$ neutrons/cm^2 s (assuming the epithermal neutron index $r = 0$)

Irradiation time, t_i (h)	Specific activity, SA_0		Radionuclidic contamination RC_0 (%)
	Ho (Ci/g)	Ho (Bq/kg)	
3	4.52	1.67×10^{14}	3.8×10^{-3}
6	8.70	3.22×10^{14}	6.4×10^{-3}
12	16.15	5.97×10^{14}	9.4×10^{-3}
18	22.52	8.33×10^{14}	1.1×10^{-2}
24	27.98	1.03×10^{15}	1.2×10^{-2}
36	36.64	1.35×10^{15}	1.3×10^{-2}
48	42.99	1.59×10^{15}	1.3×10^{-2}

Experimental

After irradiation of a holmium oxide target, the colloidal citrate solution was obtained according to the reactions:

$$Ho_2O_3 + 6HCl \longrightarrow 2HoCl_3 + 3H_2O$$

$$HoCl_3 + Na_3C_6H_5O_7 \longrightarrow HoC_6H_5O_7 + 3NaCl$$

The colloid at pH = 4.7 was stabilized by dextran grade C (m_r 60 000 to 90 000). The particle size was evaluated by optical microscopy and the colloid charge by ascending capillarity [10]. Radiochemical

*Paper presented at the Second International Conference on the Basic and Applied Chemistry of f-Transition (Lanthanide and Actinide) and Related Elements (2nd ICLA), Lisbon, Portugal, April 6–10, 1987.

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0020-1693/87/$3.50

TABLE II. Main Characteristics of ^{165}Dy, ^{166}Ho and ^{169}Er for Synoviotherapy

Nuclide	Half-life (day)	β^- radiation max. energy (MeV)	Size (nm)	Chemical form	Knee absorbed dose (rad) (1 mCi)	Whole body absorbed dose (rad) (1 mCi)	Absorbed dose whole body/knee (%)
^{165}Dy	0.097	1.30	500–5000	FHMA	32.17	1.41×10^{-3}	4.38×10^{-3}
^{166}Ho	1.12	1.85	500–10000	citrate	572.5	1.78×10^{-2}	3.11×10^{-3}
^{169}Er	9.40	0.34	10	citrate	694.9	9.30×10^{-5}	1.34×10^{-5}

purity, *i.e.*, the presence of $^{166}Ho^{3+}$ was checked by chromatography paper using acetone:water:hydrochloride (70:20:10) as solvent.

Radiation Absorbed Dose Calculation

The general equation for radiation absorbed dose D is:

$$D(\text{rad}) = 1.44 \times (A_0/m) \times T \times \sum_j \Delta_j f_j$$

where A_0 is the activity (μCi), m is the mass of target region (g), T is the effective half-life (h), f_j is the absorbed fraction, and $\Delta_j = 2.13 n_j E_j$ (n_j = mean number of photons per disintegration of jth radiation, E_j = energy of jth radiation in MeV). In SI units D is expressed in Gy (1 Gy = 100 rad). Radiation absorbed dose for ^{166}Ho was calculated assuming the 'simple model' (*i.e.*, ideal biological conditions) and introducing a few simplifications in the energy values and the absorbed fractions [11]. The radiation absorbed dose on the knee and the whole body due to ^{166}Ho, ^{165}Dy and ^{169}Er, as well as other main characteristics, are presented in Table II.

Discussion

Holmium-166 citrate is a colloid whose particle size is similar to that of ^{165}Dy/ferric hydroxide macroaggregates (FHMA). Nevertheless ^{165}Dy has a very short half-life (2.33 h) which limits its application. In fact, the chemical processing involved in the preparation of ^{165}Dy/FHMA, quality control, transport and formulation for injection takes a few half-lives. Therefore it could only be used at nuclear medicine centres close to nuclear reactors. Holmium-166 has a half-life of 26.8 h, which overcomes this problem. Erbium-169 citrate is a colloid with small particle size, which could be disadvantageous because small particles are usually associated with leakage away from the injected point. According to Table II the percentage of radiation absorbed dose 'whole body/knee' slightly favours ^{166}Ho when compared with ^{165}Dy. However, ^{169}Er exhibits a more favourable value. From Table II it is possible to know what each radionuclide can provide in terms of radiation absorbed dose to the knee, and in terms of disadvantageous dose to the whole body. The values of radiation absorbed dose rate as a function of the decay time for ^{165}Dy, ^{166}Ho and ^{169}Er are shown in Fig. 1, which visualizes the total absorbed radiation dose in terms of acute, medium or long exposure. Only clinical application could determine the most suitable radiocolloid and it would then be possible to establish the relationship between clinical effects and nuclear, physical and chemical characteristics.

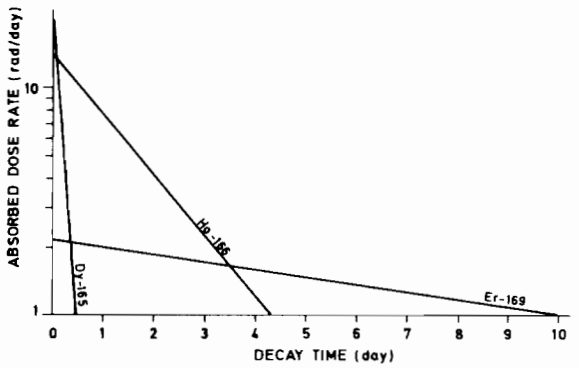

Fig. 1. Radiation absorbed dose for ^{165}Dy, ^{166}Ho and ^{169}Er per mCi administered.

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