Kinetics of Ruthenium in Humans

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INTRODUCTION

The radioactive isotopes of ruthenium with mass numbers 103 and 106 are common fission products and may represent a radiological hazard for the population in case of their release into the environment and transfer to the food chain. ^{103}Ru, having a half-life of 39.26 d, decays by β^- emission onto ^{103}Rh. ^{106}Ru ($T_{1/2}$=374 d) is a pure β^- emitter, and its daughter nuclide, ^{106}Rh, is radioactive as well. Their main emissions are given in Table I.

TABLE I
Main emission of ^{103}Ru, ^{106}Ru, and ^{106}Rh. [1]

NUCLIDE	Beta		Gamma		X-rays	
	Endpoint energy (keV)	Relative intensity	Energy (keV)	Relative intensity	Energy (keV)	Relative intensity
^{103}Ru	227	0.922	497	0.909	20.22	0.059
	113	0.066	610	0.0575	20.07	0.031
			444	0.0327	2.70	0.025
^{106}Ru	39.40	1	/	/	/	/
^{106}Rh	3541	0.786	512	0.20	21.18	0.0015
	2407	0.100	622	0.0993		
	3029	0.081	1050	0.0156		

They are produced in relevant amounts during fission processes, and can also represent a problem for nuclear waste disposal [2]. Longley and Templeton [3] report that the radionuclides of ruthenium contribute to about 60% of the beta activity released into the environment from aqueous wastes. After the Chernobyl accident, the activity concentration of these radioisotopes in the air and on the ground was similar to those of ^{131}I and ^{137}Cs [4-8]; the same was found also after other, although less dramatic, accidents [9, 10]. Particular interest was attracted by the detection of so-called "hot particles", i.e. particles with very high specific activity, even at very large distances from the site of the accident. The radiological hazard of these highly active particles is related mainly with skin deposition [11] and ingestion; inhalation doesn't seem to be a relevant incorporation pathway, also due to the dimensions of the particles [12].

The radiation dose delivered by a radioactive substance incorporated into the human body cannot be measured directly. It must be calculated on the basis of models. The biokinetic models, describing the absorption of the radioactive material into the systemic circulation, its distribution and retention in the internal organs, and its excretion mechanisms, play undoubtedly a relevant role, since they provide the primary input information for the calculation algorithm. As for many other elements of radiological significance, there is however only limited valuable knowledge for the set-up of a reliable model for ruthenium. The only human data considered for the set-up of the model currently recommended by the International Commission on Radiological Protection ICRP[13] are those presented in one work by Yamagata et al. [14], where intestinal absorption, whole body retention and excretion patterns were investigated using radioactive ^{103}Ru as a tracer. The experiments were performed at different times on the same subject, by oral administration of the tracer in three different forms: 1) as metabolized ruthenium in shellfish (first administration), 2) as not metabolized chloro complexes of nitrosylruthenium(III) (second administration) and 3) as ruthenium(III-IV) chloride complexes (third administration). No other data from controlled studies on humans are available to our knowledge. This is mainly due to the justified limitations on the use of radiotracers in humans, and to the difficulties inherent with this kind of tracer kinetic studies.

As shown in another contribution to this conference [15], the use of stable isotopes for biokinetic investigations represents an ethically acceptable methodology, being it free from any radiation risk for the volunteer subjects. In this work, the results obtained in 5 investigations conducted on two healthy volunteers are given and compared to the predictions of the ICRP model. Modifications to the model structure and to its parameters are suggested, and the dose coefficients calculated after such modifications.

EXPERIMENTAL

Stable tracers.

Ruthenium-101 metal powder (enriched to 97.8 % abundance) was purchased from Chemotrade GmbH (Düsseldorf, Germany). The following procedure was used to dissolve the metal:

10 mg of metallic ruthenium was weighted in a zirconium crucible with approx. 1.4 g potassium hydroxide and 0.14 g potassium nitrate and heated for 45 minutes at 520 °C in a muffle furnace. The cooled melt was then dissolved in water to the desired final volume. In order to retain its stability, the solution was briefly heated after addition of few drops of concentrated HCl. Ruthenium is present in the form of chloride complexes having formula $[RuCl_n(H_2O)_{6-n}]^{(n-3)-}$, predominantly with n = 4.

Two solutions of ^{101}Ru were prepared as described above, one for the oral administration and the other for intravenous application with concentrations of 309 mg $Ru \cdot l^{-1}$ and 29.4 mg $Ru \cdot l^{-1}$ respectively, as measured by Inductively Coupled Plasma Mass Spectrometry (ICP-MS). The injection solution was sterilised, and single doses were aliquoted into individual, sterile ampoules and then sealed.

Tracer kinetic investigations.

Kinetic investigations were conducted according to the protocol approved by the Ethical Committee of Technische Universität München. The detailed experimental schedule is given in Table II. The investigations were started in the morning, with the subject fasting from the evening before. One total 24-h urine sample was collected prior to the experiment (blank value). Also one blank blood sample was taken before the isotope administration. Injection was performed into a vein of the arm opposite to that used for sampling. Two hours after administration, the subject consumed a standard continental breakfast, consisting of black coffee and 2 rolls with butter and jam. Up to 8 blood samples were collected at fixed times until 10 hours post administration (24 hours in the case of injection). Total renal excretion was collected for the following intervals: 0-12 h, 12-24 h, and 24-48 h.

TABLE II
Experimental schedule.

SUBJECT	EXPERIMENT	AMOUNT GIVEN (μg ^{101}Ru)	TYPE OF ADMINISTRATION
1	1	210	intravenous injection
	2	1780	oral with ascorbate
	3	843	oral with citrate
2	4	1780	oral with citrate
	5	843	oral with ascorbate

Sample analysis

Blood plasma was separated from whole blood by centrifugation, and then stored frozen until analysis. Concentration of ruthenium in plasma was measured by means of activation analysis. The technique, described in detail elsewhere [16], is here only briefly summarized.

After addition of a known amount of ^{51}V, which is used as an internal standard, plasma samples were heated to dryness, powdered in an agate mortar and compressed to form a self-supporting tablet. For each experiment, one standard sample was also prepared from a pool plasma of healthy subjects, to which known amounts of ^{101}Ru, taken from the solution used for that administration, and of ^{51}V were added. Activation of the samples was performed with the proton beam of the Philips Cyclotron at the Paul Scherrer Institut in Villigen (Switzerland). Each sample, protected by two aluminized mylar foils, was put into individual aluminium frames and fixed to a rotating disc placed in an irradiation chamber. Up to 39 samples can be activated under the same experimental conditions, as the disc rotates at a speed of approximately 70 rounds per minute, placing one sample after the other in front of the beam line. On the basis of the optimization work previously performed [17], the nuclear reaction chosen for the determination of the ruthenium tracer is $^{101}Ru(p,n)^{101m}Rh$. The reaction product has a half-life of 4.34 d, and can be selectively determined in the activated sample through the measurement of its gamma-emission at 306.9 keV. Under these experimental conditions, ^{51}Cr is produced via activation on the internal standard ^{51}V; it decays with a half-life of 27.7 days, its main gamma emission has an energy of 320 keV. The samples were left to cool for few days, in order to allow the short-lived component of the gamma background originating from the activated biological matrix to decay, and then they were measured with high purity germanium detectors connected to a PC through multichannel buffer cards (EG&G Ortec, model 916A MCB). From the comparison of the intensities of the gamma lines corresponding to ^{101m}Rh and ^{51}Cr in each sample to those measured in the standard, after appropriate correction for different cooling and measurement times, the unknown values of the ^{101}Ru concentration can be determined.

The minimum detectable concentration in blood plasma, calculated according to the definition of Currie [18] as that concentration corresponding to a signal equal to 4.65 times the square root of the underlying

background signal, amounts in typical experimental conditions (beam current 8 μA for 30 h, cooling time 10 d, measurement time 20 h) to approx. 1 ng $^{101}Ru \cdot g^{-1}$.

Ruthenium isotopes in urine were measured by means of Inductively Coupled Plasma Mass Spectrometry[1].

RESULTS AND DISCUSSION

Figure 1 reports the concentration of the tracer in one subject in two cases: after intravenous injection of 210 μg ^{101}Ru (filled squares, left axis) and after oral administration of 1.78 mg ^{101}Ru (filled circles, right axis). For sake of comparison, the corresponding patterns as calculated from the ICRP model are given. In order to express the ICRP value as concentration, the volume of the plasma compartment was evaluated by fitting a bi-exponential function to the measured concentration values of the injected tracer. Several deviations are evident. After a rapid decrease, the clearance of the injected tracer from the plasma compartment slows down considerably. Please note the value at 24 hours post-administration, which is still about one half of the initial concentration. The oral tracer seems to be absorbed into the systemic circulation faster but to a lesser extent than predicted from the ICRP recommendation: the experimental values are indeed lower than expected, and peaked at around 3 hours after administration.

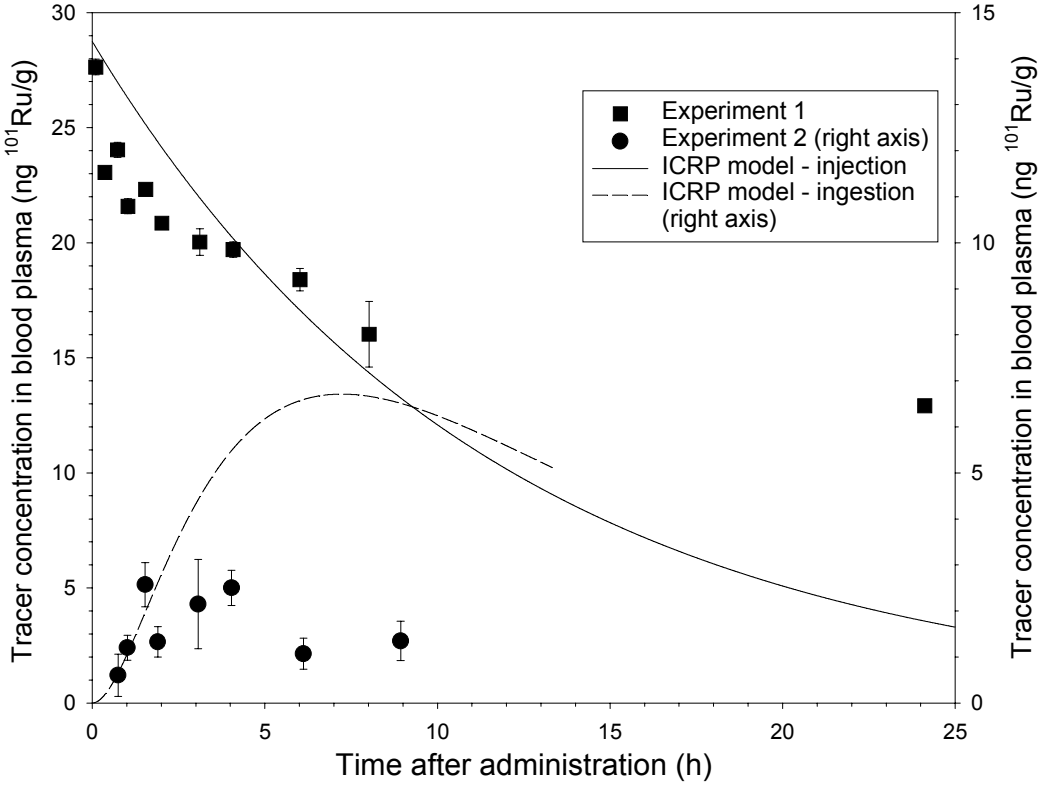

Figure 1. Tracer concentration in blood plasma after administration of ^{101}Ru in two experiments: 1) intravenous injection (filled squares, left y-axis) and 2) oral dose (filled circles, right y-axis). The corresponding time curves of the tracer concentration as predicted by the ICRP model are also given (full line: injection, broken line: ingestion).

Figure 2 shows the percentage cumulative excretion for Exp. 3 and 5. Similarly, the prediction of the model is not correspondent to the measured data: the excretion is highly overestimated, expecially with concern to the inital rise.

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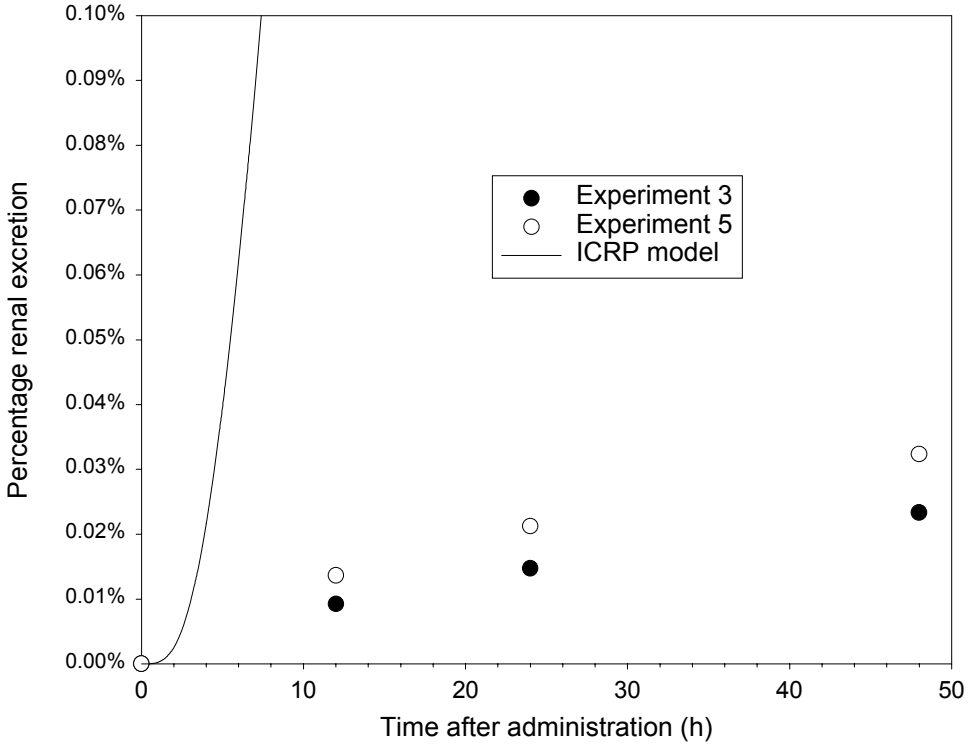

Figure 2. Percentage renal excretion over two days measured in two subjects, compared to the ICRP model prediction.

The model structure and the values of its parameters need therefore to be modified in order to provide a more correct description of the experimental measurements. A compartmental analysis approach was used, trying to keep a scheme similar to that adopted by ICRP with the same assumption of first-order kinetics. The parameters describing the intestinal absorption process were determined by fitting the model equations to the measured concentrations in blood plasma, using the modelling software SAAM II (SAAM Institute Inc., Seattle USA). The f_1-value, i.e. the fraction of incorporated activity absorbed into the circulation, was found to range between 0.0070 +/- 0.0018 and 0.0108 +/- 0.0015, against the value of 0.05 as given by ICRP. The characteristics emptying times of the stomach and of the small intestine are shorter, as is to be expected by ingestion of liquids. This modified set of parameters is also able to describe successfully the measurements in urine, provided that the direct excretion pathway from the transfer compartment to the bladder is removed. The percentage of the oral tracer excreted over 48 hours amounts to 0.034 % according to the modified model, with the experimental values ranging between 0.023 % and 0.034 % (0.77 % in the ICRP model).

The modifications introduced in the model may evidently affect the calculation of the dose coefficients. Thus dose estimates for ^{103}Ru and ^{106}Ru according to the suggested model have been compared to the ICRP ones. The number of transformations in each source organ was calculated applying the SAAM II software. The contribution of ^{106}Rh was calculated using the same biokinetic parameters as for Ru. The specific effective energy values for each combination of source and target regions were obtained by means of the SEECAL code from Christy and Eckerman. The correctness of this procedure was first tested using the current ICRP model and its parameters to obtain the dose coefficients. Whereas for ^{106}Ru the dose estimates coincide with the values published in ICRP67, several disagreements are found for ^{103}Ru. Being the model structure and the procedure employed identical for both isotopes (apart from the half-life), there is at the moment no reasonable explanation for such difference. For sake of uniformity, the dose coefficients obtained with the modified parameters were compared with those obtained in this work with the ICRP model, although different from those published.

The effective dose coefficients are in both cases slightly lower than the ICRP values: - 4 % for ^{103}Ru, - 14 % for ^{106}Ru/^{106}Rh. This is evidently due to the reduction in the value of activity which is deposited in the internal organs. However, given the low f_1-value, the main contribution to the effective dose is ascribable to the walls of the gastro-intestinal tract: for ^{103}Ru, colon and stomach account for 65 % and for 5.8 % respectively of the total effective dose according to ICRP. With the revised parameters the contribution of colon is slightly higher (71.5 %), for stomach smaller (3.8 %), mainly due to the shorter gastric emptying time introduced. For

$^{106}Ru/^{106}Rh$, the values are 78 % and 5.4 % for ICRP, 92% and 2.7 % for the modified model. Among the other organs, relatively high doses are given to the ovaries (their contribution to the total dose is as high as 20% for ^{103}Ru) and in general to all other organs which are located near the intestine.

CONCLUSIONS

The results of preliminary tracer kinetic investigations in humans have indicated a series of deviations from the prediction of the model currently recommended by ICRP especially with regard to the absorbed fraction and to the excretion rates of systemic activity. Given the low f_1-values of ruthenium, the modifications introduced in the model on the basis of these data do not substantially affect the dose coefficients as given in ICRP Publication 67. However, the consistent differences observed in the excretion patterns may be critical for a correct interpretation of bioassay measurements.

On the basis of these results and considerations, a new series of investigations has been planned with the aim to better characterize the clearance from the plasma compartment and the renal excretion also at larger time after incorporation.

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