The Toxicologic Evaluation of Radio-Pharmaceuticals

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In considering the potential toxicity of radio-pharmaceuticals, both chemical toxicity and radiation effects must be evaluated.

Most modern radio-pharmaceuticals utilize "tracer" techniques and the mass administered is so minute that pharmacologic response is difficult to detect. Radio-Pharmaceutical agents are usually administered on a "single-dose" basis and they are not intended for chronic administration. Typical administered doses of various radio-pharmaceuticals are summarized in Table I.

Table I

Radio-Pharmaceuticals-Typical Administered Mass

Agent	Nuclide	uCi Dose	Mg. Administered	
			Compound	Nuclide
Radio-Iodinated Serum Albumin	I-131	5	10.0	
Chlormerodrin	Hg-131	700	2.4	
Cyanocobalamin	Co-60	0.5	6.7×10^{-4}	
Sodium Iodohippurate	I-131	8	1.6×10^{-2}	
Oleic Acid	I-131	25	60.0	
Sodium Iothalamate	I-131	50	0.17	
Sodium Chromate	Cr-51	50		2×10^{-4}
Sodium Iodide	I-131	50		2×10^{-7}
Ferric Chloride	Fe-59	5		3×10^{-4}
Sodium Phosphate	P-32	10000		0.4
Sodium Chloride	Na-22	5		2.5×10^{-3}

Table II

Radio-Pharmaceuticals—Acute Toxicity Safety Factors

Product	Typical Human Dose*			Sub-Lethal Does in Mice (ml/kg)	Acute Safety Factor
	μCi	ml	ml/kg		
Cesium Chloride Cs13-1	1250	1.67	0.033	22.5	682
Chlormerodrin Hg-203	700	1.75	0.035	25.0	714
Sodium Pertechnetate Tc99m	10000	4.0	0.08	100.0	1250
Sodium Iothalamate I-131	300	1.0	0.02	27.5	1375
Colloidal Gold Au-198	150	0.83	0.017	25.0	1471
Technetium Sulfide Tc99m	3000	1.5	0.03	50.0	1667
Macro aggregated Albumin I-131	300	0.3	0.006	25.0	4167

* Human does based upon the administration of typical radio-pharmaceutical formulations.

The small administered mass is directly related to the large safety factors established for radio-pharmaceuticals. Table II summarizes calculated factors based on typical doses to man and acute intravenous toxicity studies in mice. Because of physical decay of the radionuclide, the required injection volume must increase with time in order to administer a given amount of radioactivity. This decay factor can be significant with pharmacologically-active compounds labeled with short-lived nuclides; e.g., Chlormerodrin Hg 197.

Often the preservative required in multiple-dose containers is the most toxic constituent in the radio-pharmaceutical formulation. Table III summarizes the result of comparative acute toxicity studies with a common preservative, 0.9% benzyl alcohol, and typical radio-pharmaceutical formulations. Results indicate that the benzyl alcohol per se accounts for much of the acute toxicity.

Table III

Radio-Pharmaceuticals—Preservative Toxicity

Product	Sub-Lethal Dose in Mice (ml/kg)	Preservative (0.9% Benzyl Alcohol)	Toxicity Ratio (Benzyl: Product)
0.9% Benzyl Alcohol (in isotonic NaCl)	30.0	—	—
Sodium Iothalamate I-131	27.5	Yes	1.09
Colloidal Gold Au-198	25.0	Yes	1.20
Macro Aggregated Albumin I-131	25.0	Yes	1.20
Chlormerodrin Hg-203	25.0	Yes	1.20
Cesium Chloride Cs-131	22.5	Yes	1.33
Sodium Pertechnetate Tc99m	100.0	No	0.3
Technetium Sulfide Tc99m	50.0	No	0.6

With radionuclidic material, the stable nuclide formed during decay may be the subject of toxicologic evaluation. Studies have been carried out with ^{99}Tc which is the stable, but radioactive, decay product of ^{99m}Tc. ^{99}Tc is a beta emitter (0.295 Mev) with a half-life of 2.1×10^{5} years. Acute intravenous toxicity studies in mice with solutions of sodium petrtechnetate ^{99}Tc indicate an approximate LD_{50} of 66 mg/kg, or 1125 μCi/kg of ^{99}Tc. Appropriate calculations indicate that 1 mCi of ^{99m}Tc decays to form 3.4×10^{-9} μCi of ^{99}Tc.

The maximum amount of ^{99}Tc which might be injected, or formed, during a brain scanning dose of sodium pertechnetate ^{99m}Tc was estimated by making the following pessimistic assumptions:

1. The brain-scanning dose of Sodium Pertechnetate ^{99m}Tc is 10 mCi.
2. Ten half-lives elapse, for ^{99m}Tc, from reactor to patient.
3. No ^{99}Tc is excreted following injection.

The amount of ^{99}Tc injected would then equal 3.58×10^{-5} μCi or 7×10^{-7} μCi/kg in a 50 kg human. On this basis, the acute safety factor of ^{99}Tc, as compared in intravenous administration in mice, would equal approximately 1.5 billion ($1125/7\times10^{-7}$).

Excretion studies in rats indicate that ^{99}Tc sodium pertechnetate is excreted at a relatively rapid rate following intravenous injection. Twenty-four hours post-injection, the percent of injected dose remaining was: 0.15% —lungs, 0.95%—liver, 0.02%—spleen, 0.33% —kidneys, 0.01%—testes, 0.03%—brain, 19.05 %—remaining carcass. A significant amount of ^{99}Tc was found in hair and skin. Whole-body assay of mice for ^{99}Tc indicates approximately 1% of the dose remaining 70 hours following intravenous injection.

In the evaluation of Chlormerodrin ^{203}Hg, it was shown that specific activity and administered dose can have significant effects upon distribution and excretion. Data summarized in Table IV indiate that in rats an

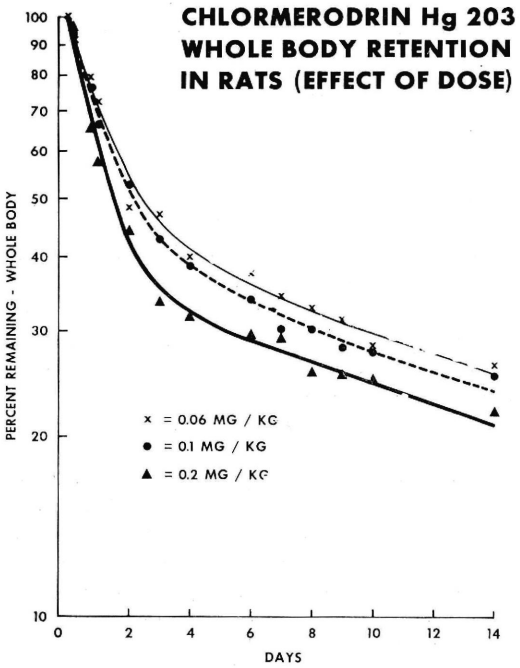
increasing dose of intravenously administered Chlormerodrin ^{203}Hg, with decreasing specific activity, can significantly reduce the percent uptake of ^{203}Hg in the kidneys. Figure I demonstrates a significant decrease in biological half-life as the mass administered increases from 0.06 mg/kg to 0.20 mg/kg of Chlormerodrin ^{203}Hg.

Table IV

Chlormerodrin Hg-203—Effect of Specific Activity on Kidney Uptake

Chlormerodrin Administered			Percent of Injected Dose	
μCi	mg/kg	μCi/mg	Kidneys	Liver
7.03	0.8	87.8	19.5	0.33
7.03	1.7	20.7	8.7	0.22
7.03	2.9	12.1	2.6	0.19
7.03	6.6	5.3	2.3	0.39
7.03	12.9	2.7	0.75	0.40
7.03	24.2	1.5	0.8	0.68

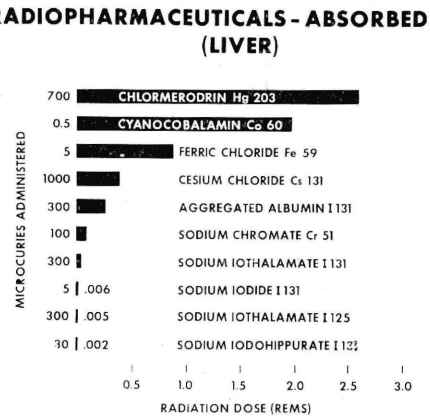
200 Gm Rats; i. v. injection; sacrificed 24 hours post-injection



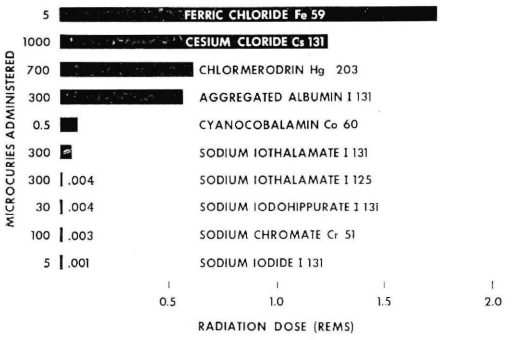
Clinical efficacy of existing radio-pharmaceuticals is based upon radiation and, in making a toxicologic evaluation of them, the radiation dose delivered must be a primary consideration.

Existing literature has been reviewed and extensive animal studies have been carried out in order to obtain data relating to nuclide decay schemes, biological distribution, and biological half-life.

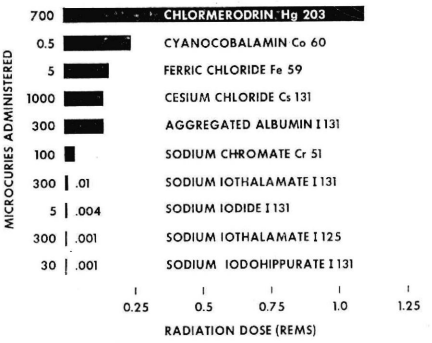
Radiation dose was calculated using equations derived from those presented in the report of the International Commission on Radio-logical Protection, Committee II(1). Results of these calculations are summarized in Figures II through VI.



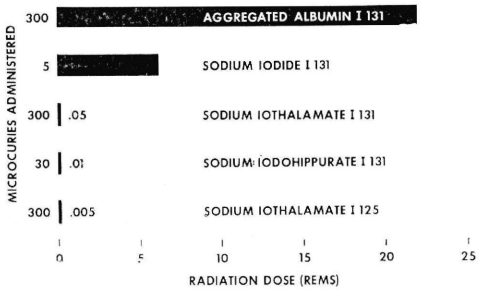
RADIOPHARMACEUTICALS - ABSORBED DOSE (TESTES)



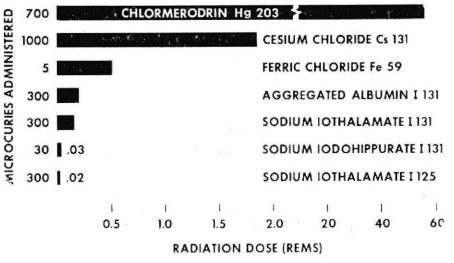
RADIOPHARMACEUTICALS - ABSORBED DOSE (WHOLE BODY)



RADIOPHARMACEUTICALS - ABSORBED DOSE (THYROID)



RADIOPHARMACEUTICALS - ABSORBED DOSE (KIDNEYS)



Radiation dose figures shown are pessimistic in that the highest percent of nuclide found in any tissue was used to represent nuclide concentration (μCi/gm). The absorbed radiation dose is calculated assuming typical amounts of radioactivity administered for clinical procedures; e.g., 700 μCi Chlormerodrin ^{203}Hg administered for brain-scanning. Data, summarized in Figure IV, are based upon results obtained in the unblocked thyroid. It is important to note that uptake in specific organs may represent the radio-nuclide only following metabolic degradation of the radiopharmaceutcial.

Radiation dose calculations summarized in this paper are estimates based upon the extrapolation of animal data to man. Recently, specialized groups and committees have been organized to specifically study the radiation dosimetry of radio-pharmaceuticals. One such committee, the Medical Internal Radiation Dose Committee (MIRD) of the Society of Nuclear Medicine is concentrating upon the acquisition of pertinent data in humans so that a more precise estimation of radiation dose may be made. A new method for computing absorbed dose has been developed by Loevinger and Berman, and a mathematical formalism, based upon this work, has been published by MIRD (2).

References

1. Recommendations of the International Commission on Radiological Protection, I.C.R.P., Publication 2, "Report of Committee II on Permissible Dose for Internal Radiation," Pergamon Press, London, England (1959); Health Physics, 3, 1 (1960).
2. Loevinger, R., and Berman, M., A Schema for Absorbed-Dose Calculations for Biologically-Distributed Radionuclides, MIRD /Pamphlet No. 1, J. Nuclear Med., MIRD Supplement Number 1, February (1968).