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Internal Dosimetry Studies of Radiopharmaceuticals; I. Tolpovidone ^{131}I[1]

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The distribution and effective half-life of Tolpovidone ^{131}I was determined in two species, namely rats and cats. These data were then extrapolated to man to calculate the internal radiation dose delivered during the diagnostic use of Tolpovidone ^{131}I

This communication will show the levels of radiation expected in whole body and various organs following the intravenous administration of Tolpovidone ^{131}I to man. Radiation doses reported are based upon the administration of either a 30 μc dose or a 500 μc dose to man. The 30 μc dose represents a typical upper level used to diagnose hypoalbuminemia (1) while the 500 μc dose is currently under investigational use in brain-scanning techniques (2,3).

This communication will also compare the radiation dose delivered during the diagnostic use of Tolpovidone ^{131}I with maximum permissible occupational exposure limits as recommended by the National Committee on Radiation Protection (4) and the International Commission on Radiological Protection (5).

MATERIALS AND METHODS

The distribution of Tolpovidone ^{131}I was studied in adult rats and cats. Effective half-life was determined using a Packard-Armac scintillation detector. Due to the size of the detector chamber, it was necessary to use kittens instead of adult cats to determine effective turnover in the cat.

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[1]Raovin®-131, Abbott Laboratories, North Chicago, Illinois and Oak Ridge, Tennessee. This product is a purified copolymer having an average molecular weight approximating 40,000 and consisting of vinylpyrrolidone and a fixed ratio of p-toluidine. Carrier-free $Na^{131}I$ is reacted chemically with this purified material to form a stable bond between the ^{131}I and the copolymer.

[2]Nucleonics Laboratory, Abbott Laboratories.

Formulae used in calculating radiation dose were taken from the report of I.C.R.P. Committee II (6) as follows: $q = \frac{2.8 \times 10^{-3} mR}{f_2 \mathcal{E}}$ where: q represents the body burden of the radionuclide in microcuries, f_2 is the fraction of radionuclide in organ of that in total body, R is the dose rate in rem per week, m is the mass, in grams, of the organ of reference, and $\mathcal{E}$ is the effective energy per disintegration of the radionuclide.

By rearranging, simplifying and integrating from zero to infinity, the above equation becomes:

$$\textit{Total Dose } \beta + \gamma \textit{ (rems)} = \mathcal{E} \times \frac{357}{7} \times \frac{qf_2}{m} \times \frac{T}{.693} \text{ where:}$$

T = Effective half-life, in days, of the radionuclide.

For the case where the radionuclide is not disappearing at a constant rate, this equation would then become:

$$D_{\beta+\gamma\ (rems)} = \mathcal{E} \times \frac{357}{7} \times \frac{qf_2}{m} \left(f_a \frac{T_a}{.693} + f_b \frac{T_b}{.693} \textit{ etc.}\right).$$

Here f_a, f_b, T_a, T_b represent fractional parts and effective half-lives of each component part of the disappearance curve.

The effective energy per disintegration, $\mathcal{E}$, can be calculated according to empirical equations given in the report of the I.C.R.P. Committee II (6). This effective energy term is dependent upon the decay scheme of the radionuclide, tissue absorption coefficients, effective radius of the body organ, etc. Pertinent physical data used in calculation of $\mathcal{E}$ are shown in Table I and calculated values of $\mathcal{E}$ for ^{131}I are shown for various organs in Table IV.

TABLE I

PHYSICAL CONSTANTS USED FOR CALCULATION OF EFFECTIVE ENERGY, $\mathcal{E}$ (7)

Emissions	*Energy mev*	*Fraction f*	*Tissue Absorption Coefficient*	*Internal Conversion K shell*
β_1	.250	.028		
β_2	.335	.093		
β_3	.608	.872		
β_4	.815	.007		
γ_1	.722	.028	.033	.0028
γ_2	.637	.093	.034	.0037
γ_3	.364	.872	.033	.018
γ_4	.164	.007	Ignored	

Binding energy, η, for product nuclide, Xe, = .035 mev.

For purposes of calculating radiation dose, the highest concentration found in any organ, rat or cat, was used as the initial concentration, $\frac{qf_2}{m}$. Initial whole body retention was assumed to equal 100 percent of the injected dose. Radiation dosages were calculated from total body effective half-life as determined in the cat. Effective half-life in individual body organs was assumed to be the same as total body half-life. Strictly speaking, the effective half-life of Tolpovidone ^{131}I in individual body organs might be different from total body half-life, although organ data shown in Table II do not indicate any great differences.

RESULTS

A. *Concentration or Tissue Distribution*

1. *Rats:* Six male rats (avg wt = 409 gm) were injected intravenously with 5.3 μc (0.24 mg) Tolpovidone ^{131}I (lot No. VP-069-9) in 0.5 ml 5% Dextrose solution.

Animals were sacrificed after 4, 8, 24, 48, 72 and 96 hours and tissue concentrations determined. Table II summarizes these distribution studies.

2. *Cats:* Two male adult cats (wt 2.5 and 1.9 kg) were intravenously injected with 13 μc (0.84 mg) per kg of Tolpovidone ^{131}I (lot No. VP-089-19). Animals were anesthetized with 30 mg/kg sodium pentobarbital[1] intraperi-

TABLE II

TISSUE DISTRIBUTION OF TOLPOVIDONE ^{131}I IN RATS

	% of Total Recovered Activity					
Organ	*4 hrs*	*8 hrs*	*24 hrs*	*48 hrs*	*72 hrs*	*96 hrs*
Thyroid	0.29	0.28	0.86†	0.38	0.34	0.48
Liver	8.30	6.51	9.05	10.58†	9.35	8.41
Kidneys	3.15†	1.89	0.94	0.75	0.89	0.62
Spleen	0.49	0.38	0.56	1.01	1.03†	0.99
Heart	0.47	0.38	0.56†	0.20	0.19	0.15
Testicles	0.46	0.48†	0.34	0.29	0.37	0.23
Urine	25.18	37.00	45.15	47.99	48.12	52.85
Feces	Nil	0.12	1.10	3.16	6.35	3.74
G. I. Tract	5.70	4.81	6.17†	5.50	4.25	4.41
Carcass	55.90	48.14	35.22	30.14	29.11	28.14
% Injected Dose Recovered	97.0	106.1	103.0	96.74	106.8	104.2
Animal Wt (gm)	405	370	370	438	460	410

†Highest concentration found.

[1]Nembutal®, Abbott Laboratories, North Chicago, Illinois.

toneally in order to facilitate intravenous injection. These animals were sacrificed at 8 and 24 hours and tissue concentrations of ^{131}I determined. Table III summarizes these distribution studies.

B. *Turnover Studies*

1. *Rats:* Nine male rats (avg wt 214 gm) were injected intravenously with 0.49 μc (.024 mg) Tolpovidone ^{131}I and each was counted periodically via a liquid scintillation detector to determine the rate of disappearance of drug. The average values for these nine animals are shown in Fig. I.

Graphic resolution of the observed disappearance curve (Fig. I) into its component parts yielded three components with initial fraction of total dose and effective half-lives as follows: $f_a = .255$, $T_a = 0.3$ days; $f_b = .065$, $T_b = 2.0$ days; $f_c = .68$, $T_c = 6.86$ days.

2. *Cats:* Two female cats (wt 510 gm) were injected intravenously with 0.5 μc (0.024 mg) Tolpovidone ^{131}I and each kitten was counted periodically to determine rate of disappearance of the drug. The animals were anesthetized with 30 mg/kg of sodium pentobarbital intraperitoneally to facilitate injection.

Figure 2 shows the disappearance of ^{131}I in the kittens. The curve was resolved into its components are previously described yielding three components with initial fraction of total dose and effective half-lives as follows: $f_a = .145$, $T_a = 0.21$ days; $f_b = .042$, $T_b = 1.6$ days; $f_c = .815$, $T_c = 6.5$ days. It is doubtful that these data differ significantly from rat data, since only two kittens were used.

TABLE III

TISSUE DISTRIBUTION OF TOLPOVIDONE ^{131}I IN CATS

Organ	*% of Total Injected Activity*	
	8 hrs	*24 hrs*
Thyroid	0.17†	0.07
Liver	10.83†	5.81
Kidneys	1.63†	1.39
Spleen	1.41†	0.57
Heart	0.69†	0.34
Testicles	0.04	0.08†
Brain	0.13†	0.09
G. I. Tract	10.26†	6.15
Animal Wt (kg)	1.9	2.5

†Highest concentration found.

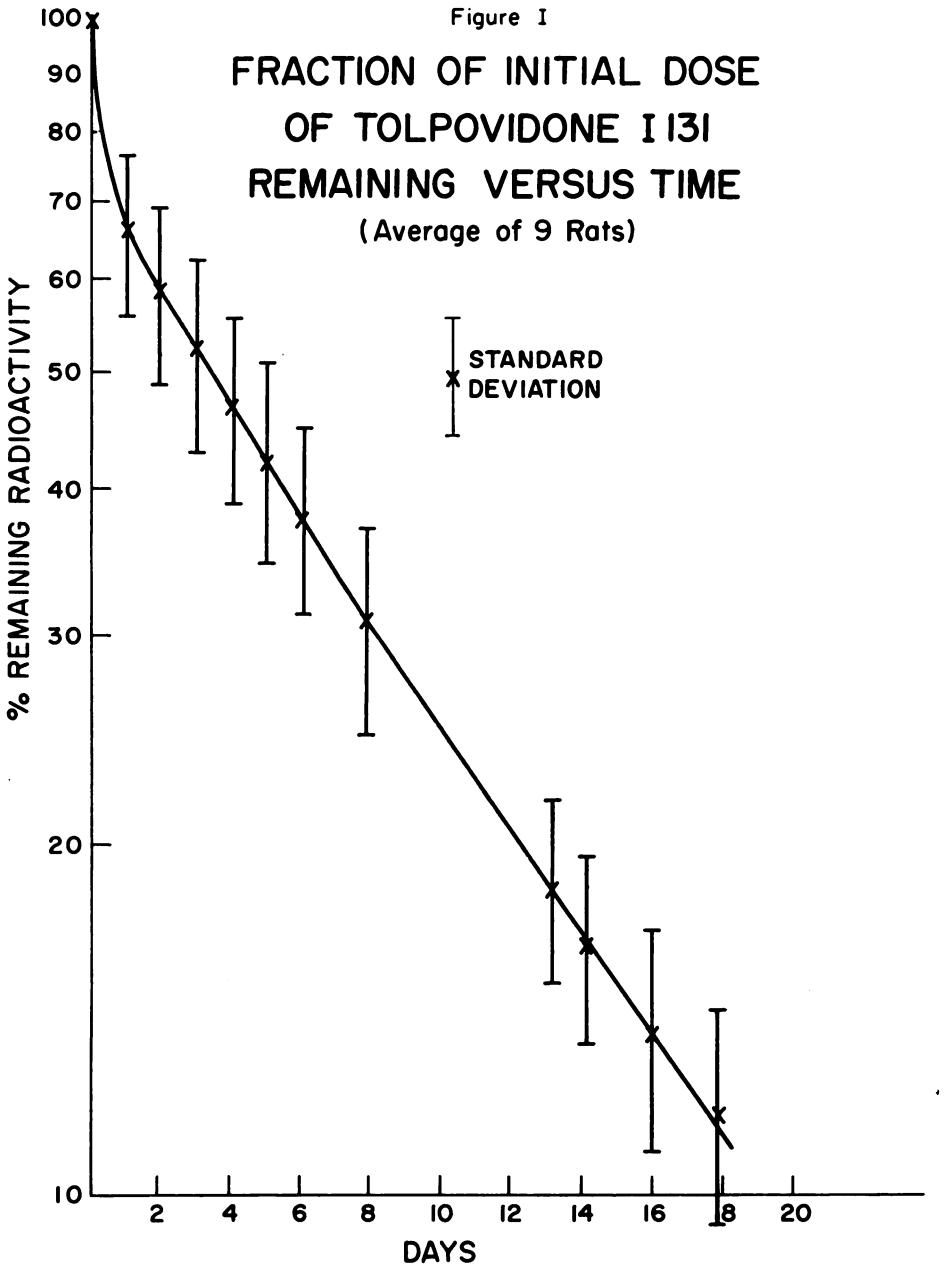

Fig. 1. Fraction of Initial Dose of Tolpovidone ^{131}I Remaining Versus Time (Average of 9 rats.).

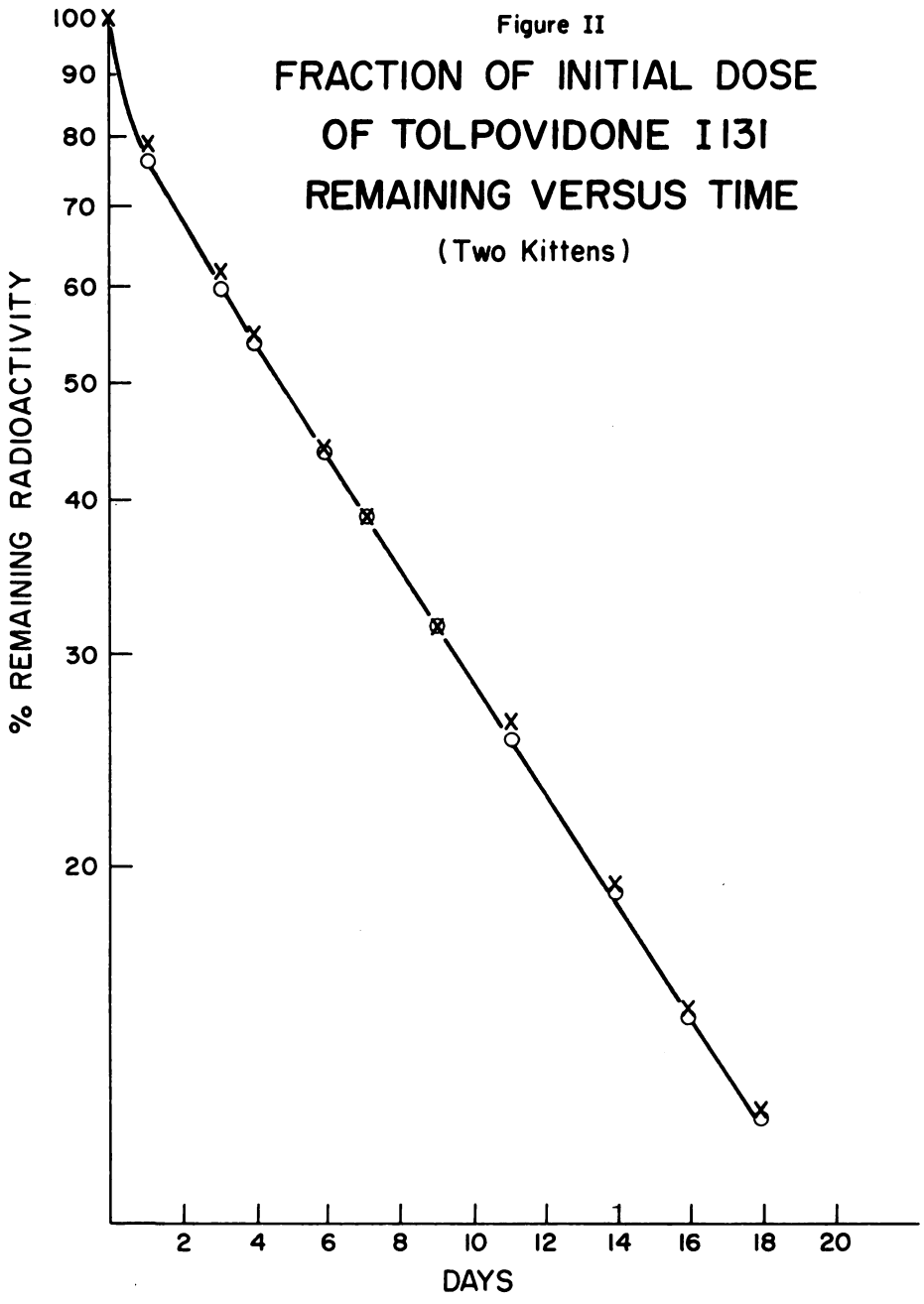

Fig. 2. Fraction of Initial Dose of Tolpovidone ^{131}I Remaining Versus Time (Two Kittens).

TABLE IV

DATA SUMMARY USED IN CALCULATION OF RADIATION DOSAGE (Q = 30 μC TOLPOVIDONE ^{131}I)

Organ	*Highest fraction of dose* f_2	*Amount with 30 μc dose -131 Raovin* qf_2 (μc)	*Organ Wt man* m (gm)	*Concen* $\frac{\mu c/gm}{qf_2}{m}$	$\mathcal{E}$	*Fraction of Total Dose & Effective Half-Life* f_a	T_a *days*	f_b	T_b *days*	f_c	$T_{c\ (cat)}$ *days*
Total Body	1.0	30	70000	.00043	.445	.145	.21	.042	1.6	.815	6.5
Kidneys	.0315 rat	0.95	300	.00317	.274	"	"	"	"	"	"
Spleen	.0141 cat	0.42	150	.00280	.274	"	"	"	"	"	"
Liver	.1083 cat	3.25	1700	.00191	.310	"	"	"	"	"	"
Thyroid	.0086 rat	0.26	20	.01300	.236	"	"	"	"	"	"
G. I. Tract	.1026 cat	3.08	2000	.00154	.445	"	"	"	"	"	"
Testes	.0048 rat	0.14	40	.00350	.236	"	"	"	"	"	"
Brain	.0013 cat	0.04	1500	.00003	.350	"	"	"	"	"	"

Data used in calculation of total radiation dose from the use of 30 μc Tolpovidone ^{131}I are summarized in Table IV. Data used in these calculations were purposely chosen so that radiation dosage would represent maximum value, i.e. calculations made using highest tissue concentrations found and greatest effective half-life factor. Table IV accounts for approximately 30 per cent of

TABLE V

ESTIMATED RADIATION DOSAGE IN MAN FROM DIAGNOSTIC USE OF TOLPOVIDONE ^{131}I

Organ	$D\beta + \gamma$ *(rems) 30 μc dose*	$D\beta + \gamma$ *(rems) 500 μc dose*
Total body	.08	1.27
Kidneys	.35	5.75
Spleen	.31	5.08
Liver	.24	3.92
Thyroid	1.22	20.30
G. I. Tract	.27	4.53
Testes	.33	5.47
Brain	.004	.07

TABLE VI

MAXIMUM PERMISSIBLE OCCUPATIONAL EXPOSURE LIMITS AND COMPARISON WITH ESTIMATED RADIATION DOSE FROM TOLPOVIDONE ^{131}I

Organ	*Maximum permissible quarterly occupational exposure limit (rems)*	*Ratio-delivered dose (Tolpovidone) to quarterly exposure limit*	
		30 μc dose	*500 μc dose*
Total Body	3	.03	.42
Kidneys	4	.09	1.44
Spleen	4	.08	1.27
Liver	4	.06	.98
Thyroid	8	.15	2.54
Testes	3	.11	1.82
Brain	4	.001	.02

total dose in cited organs while approximately 50 percent is excreted within 72 hours. The remaining 20 percent of the dose is assumed to be uniformly distributed and is not significantly concentrated in any other tissues to our knowledge.

Representative radiation doses that might be expected in man during the diagnostic use of either 30 μc or 500 μc of Tolpovidone ^{131}I are shown in Table V. Table VI gives maximum permissible occupational exposure limits, as recommended by the N.C.R.P. (4) and I.C.R.P. (5), in addition to a comparison of these limits to the radiation dose delivered during the diagnostic use of Tolpovidone ^{131}I.

DISCUSSION

The use of animal data to calculate radiation dosage in man is not the most desirable situation but adequate human data is lacking, for obvious reasons.

Our radiation dosage calculations indicate that a 30 μc dose of Tolpovidone ^{131}I, which is used to diagnose hypoalbuminemia, delivers such a slight amount of radiation that it could theoretically be used many times per year without exceeding yearly occupational exposure limits. Necessity for this extent of use would be highly unlikely and any diagnostic procedure with radiopharmaceuticals should be consistent with the concept of adequate diagnosis with minimum radiation.

Even the 500 μc brain-scanning dose of Tolpovidone ^{131}I could theoretically be used more than once without exceeding yearly occupational exposure limits. It is universally agreed, however, that unnecessary exposure to radiation should be avoided, so that the real decision here is whether the medical consequences of an undiagnosed intracranial tumor are more foreboding than the radiation delivered by a brain-scanning dose of Tolpovidone ^{131}I. It is also generally accepted that radiation doses of the magnitude delivered by 500 μc of Tolpovidone ^{131}I are too low to cause overt somatic effects and that the primary concern involves genetic changes. Possible adverse genetic changes must be balanced against the medical consequences to a patient with an uncorrected intracranial tumor.

The common practice of pre-medication with nonradioactive sodium iodide would greatly reduce the radiation dose to the thyroid (8).

SUMMARY

The distribution and effective half-life of Tolpovidone ^{131}I (^{131} Raovin) has been studied in both rats and cats. These data have been extrapolated to man to estimate the radiation dose delivered during the use of ^{131}Raovin for brain-scanning and diagnosis of hypoalbuminemia. Radiation dosage calculations indicate that a 30 μc dose of Tolpovidone ^{131}I delivers considerably less radiation than maximum permissible quarterly occupational exposure limits and that a 500 μc dose of Tolpovidone ^{131}I delivers less radiation than established yearly exposure limits.

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