DOSE ESTIMATIONS FOR RADIOACTIVE *cis*-DICHLORODIAMMINE PLATINUM (195m) II - A NEW RADIOPHARAMACEUTICAL

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1. INTRODUCTION

The inorganic antineoplastic agent *cis*-diamminedichloro platinum (II) (cis-DDP, NSC-119875) has been shown to be active as a single agent in several tumors such as those of gonadal origin (1), squamous cell carcinoma, (2),etc. and has shown promise in combination with other chemotherapeutic agents against other human solid tumors (3-5).

In view of the low therapeutic index and high toxicity (6) of this drug we feel that a rationale should be developed to determine drug administration schedules which would maximize the drug's effectiveness in an individual patient. Radiolabeled cis-DDP may serve as a useful tool in determining the appropriate pharmacokinetic parameters necessary to accomplish this task (7). Prior to using any new radioactive drug products in humans, however it is required to calculate the radiation doses expected in clinical use.

A preliminary and partial dosimetry for this drug based upon the biological data that were available at that time (8) has been published by this laboratory (9). The present work is based on a more complete analysis of the biological distribution of cis-DDP in rodents, both control and tumor bearing. Part of the biological work has been presented at the Third International Conference on Platinum Coordination Complexes in Cancer Chemotherapy (10).

This study may serve for dosimetry of patients and staff dealing with this agent. The MIRD pamphlets have not yet dealt with this radionuclide.

2. MATERIALS AND METHODS: ANIMAL DISTRIBUTION STUDIES

Male, Sprague-Dawley rats weighing 100-150g, both control and bearing solid Walker 256 carcinosarcoma, were injected with the radiolabeled cis-DDP at a dose of 1 mg/kg in normal saline by i.v. tail vein and placed in metabolic cages. At 0.5, 1, 3, 6, 12, 48 and 72 hours these animals were sacrificed and dissected. Values for percent injected activity per organ at the selected time periods for control rats are tabulated in table 1. Details on the synthesis, sampling and counting methods have been previously published (10).

3. DOSIMETRY

3.1 Basic physical parameters -

The principal physical parameters involved in the internal dose calculations for platinum-195m has been previously published (9).

3.2 Absorbed Dose Rates to Human Organs -

The absorbed doses per unit cumulated activities for 63 main source-target organ pairs are presented in table 2. These S values have been calculated using the basic physical data (9) and the absorbed fraction values from MIRD pamphlet No. 5 (11).

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3.3. Biological parameters -
The cumulated activities (μCi-h per μCi administered) in the organs were directly determined from the biological distribution studies (table 1) and are presented in table 3. These values were calculated by numerical integration of the fractional organ uptake versus time curves, using the tapezoid method

3.4 Absorbed Cumulated Doses to Reference Man -
Assuming that the biological distribution and retention functions in man will be similar or close to those in control rats, we assesed the cumulated doses to 7 principal human organs per unit activity of platinum-195m-*cis*-dichlorodiammine administered. These results are presented in table 4.

4. DISCUSSION

A definitive internal dosimetry of ^{195m}Pt *cis*-dichlorodiammine has been presented. From the results presented in table 4, it is evident that from the occupational radiation safety point of view, platinum-195m-*cis*-dichlorodiammine can be classified as a material having relatively low radiation toxicity. The critical organ is the kidney, which is also the organ where toxicity from the cold material is most significant. The organ receiving the second highest dose is the skin. Inasmuch as the skin has a relatively low radiation sensitivity, this will not present a radiation safety problem, although it does interfere with organ imaging studies of deeper organs, because of the radiation "envelope". The clinical utilization of this drug will result in radiation doses to several organs that are comparable to those delivered by a number of commonly used radiopharmaceuticals (12). Assuming that a typical procedure will involve the administration of 500 μCi for achieving the clinical results desired this will deliver a dose of the order of 2.2 Rads to the kidney, 0.5 Rads to the liver, 1.7 Rads to the skin, and a few millirads to the whole body.

It should also be noted that most of the radiation dose is due to non-penetrating radiation, and, as can be seen from table 2, the organ-organ doses are relatively small. Thus, the radiation dose to the organs with small drug uptake will be negligible. As an example, the uptake of the testes is roughly equivalent to that of the spleen (table 1), and although a direct calculation of the radiation dose to the gonads was not possible due to absence of absorbed fraction data, we can predict that the radiation dose will be of the same order of magnitude (5×10^{-4}Rad/μCi administered). Similar considerations can be made for the ovary.

The present study has provided a basis for the calculation of ^{195m}Pt dosimetry and specific dose estimations for ^{195m}Pt-cis-DDP. The radiation doses may be very different for other platinum complexes labelled with platinum-195m, because of their different retention and excretion characteristics. In addition, biological variation in the distribution and excretion of ^{195m}Pt-cis-DDP in diseased patients may also result in different radiation doses.

REFERENCES

(1) GOTTLIEB, J.A., et al., Cancer Chemotherapy Rept., 59 (Part 1): 621-628 (1975)
(2) CARDONA, F.A., et al., Wadley Bulletin, 2, No. 3, 45, July (1972)

(3) HILL, J.M., et al., Cancer Chemotherapy Reports, 59 (Part 1): 647-659 (1975)
(4) (a) HAYES, D., et al., AACR Abstracts, p. 169 (1976)
(b) MERRIN, C., AACR Abstracts, p. 243 (1976)
(5) (a) CVITKOVIC, E., et al., Proc. 3rd Intl. Conf. Pt. Coord. Compl. in CA Chemotherapy, Dallas (1976)
(b) CVITKOVIC, E., et al., Cancer Chemotherapy, Dallas (1976)
(c) CHARY, K.K., et al., Proc. 3rd Intl. Conf. Pt. Coord. Compl. in CA Chemotherapy, Dallas (1976)
(6) (a) SCHAEPPI, J., et al., Toxicol. Appl. Pharmacol., 25:230-241 (1973)
(b) TALLEY, R.W., et al., Recent Results Cancer Res., 48: 160-166 (1974)
(7) WOLF, W., et al., Proceedings of the 3rd Intl. Conf. Pt. Coord. Compl. in Cancer Chemotherapy, Dallas, Texas, October 1976, In Press.
(8) WOLF, W., et al., in: "Radiopharmaceuticals and Labeled Compounds", Vol II, IAEA, Vienna, p. 205 (1973)
(9) SCHLESINGER, T. and WOLF, W., in: Radiopharmaceutical Dosimetry, R. Cloutier, Ed., FDA-76-8044, p. 452-9 (1976).
(10) WOLF, W. and MANAKA, R.C., Proc. 3rd Intl. Conf. Pt. Coord. Compl. in Cancer Chemotherapy, Dallas, Texas, October 1976, In Press.
(11) SNYDER, W.S., et al., J. Nucl. Med. Suppl. No. 3, NM/MIRD Pamphlet 5, Society of Nuclear Medicine (1969)
(12) GREENFIELD, M.A., and LANC, R.G., "Elements of Dosimetry", Table 8.6, p. 196, in "Radiopharmacy", M. TUBIS and W. WOLF, eds., J. Wiley-Interscience, New York, N.Y. (1976).

Organ	Time (Hrs.)						
	0.5	1	3	6	12	24	72
Blood	4.72± 0.73	2.84± 0.53	2.86± 0.50	2.73± 0.35	2.46± 0.19	2.43± 0.12	2.61± 0.01
Skin	19.66± 2.41	16.37± 4.19	15.73± 1.96	15.30± 0.77	13.12± 1.78	10.56± 1.18	11.12± 0.50
Thyroid	.06± 0.01	.04± 0.01	.04± 0.01	.01± 0.00	.00± 0.00	.01± --	.00± 0.00
Liver	5.53± 0.65	4.79± 0.42	4.15± 0.40	3.93± 0.43	3.54± 0.31	3.52± 0.12	2.68± 0.25
Spleen	.20± 0.07	.17± 0.01	.20± 0.06	.14± 0.04	.13± 0.02	0.27± 0.05	.12± 0.02
Pancreas	.16± 0.04	.11± 0.02	.13± 0.03	.12± 0.03	.12± 0.05	0.13± 0.02	.10± 0.02
Stomach	.35± 0.05	.27± 0.03	.24± 0.03	.25± 0.02	.24± 0.02	0.19± 0.03	.15± 0.03
Testes	.24± 0.08	.15± 0.04	.11± 0.01	.10± 0.01	.09±<0.01	0.10±<1.01	.10±<0.01
Fat	1.31± 0.16	1.08± 0.54	.93± 0.17	.62± 0.12	.42± 0.07	0.00± --	.69± 0.17
Kidneys	3.74± 0.81	2.67± 0.26	3.48± 1.85	2.90± 0.18	2.86± 0.28	2.92± 0.14	2.62± 0.16
Adrenals	.04±<0.01	.03±<0.01	.03± 0.02	.01±<0.01	.01± 0.01	0.02±<0.01	.01±<0.01
Heart	.11± 0.02	.08± 0.02	.07±<0.01	.06±<0.01	.04± 0.03	0.07±<0.01	.05±<0.01
Lungs	.56± 0.09	.40± 0.08	.40± 0.04	.39± 0.04	.25± 0.17	0.29± 0.02	.28± 0.04
Brain	.07± 0.01	.06± 0.01	.06± 0.02	.03±<0.00	.08± 0.12	0.05± 0.02	.02±<0.01
Muscle	7.00± 1.04	5.73± 1.32	6.93± 2.37	6.50± 0.96	5.10± 2.38	5.37± 0.66	4.61± 0.36
Bone	7.68± 1.87	6.51± 1.44	6.59± 0.94	4.83± 0.78	5.18± 1.61	5.37± 0.01	3.68± 0.03
Marrow	.04± 0.01	.04± 0.01	.03± 0.00	.01± 0.00	.07± 0.11	<0.01±<0.01	.01±<0.01

TABLE 1 Tabulation of Percent Injected Dose Per Organ at Selected Time Periods for Control Rats

Target Organs \ Source Organs	Bladder	Kidney	Liver	Lungs	Spleen	Skin*	Total Body
Bladder	8.5 E-4	1.1 E-7	6.3 E-8	3.1 E-9	3.4 E-8	2.8 E-7	1.1 E-6
Bone(Total Marrow)	9.6 E-7	5.0 E-7	1.3 E-6	1.8 E-6	1.3 E-6	----	2.3 E-6
Kidney	1.1 E-7	1.5 E-3	2.5 E-6	4.6 E-7	6.0 E-6	9.8 E-8	1.1 E-6
Liver	5.6 E-8	2.5 E-6	2.4 E-4	1.6 E-6	4.9 E-7	3.0 E-7	1.1 E-6
Lung	1.3 E 9	4.8 E-7	1.8 E-6	4.2 E-4	1.6 E-6	3.2 E-7	9.9 E-7
Spleen	4.9 E-8	6.2 E-6	1.3 E-6	1.5 E-6	2.4 E-3	3.0 E-7	1.1 E-6
Skin	2.8 E-7	9.8 E-8	3.0 E-7	3.2 E-7	3.0 E-7	2.1 E-4**	3.8 E-7
Uterus	1.3 E-5	4.3 E-7	1.9 E-7	2.3 E-8	1.9 E-7	----	1.2 E-6
Total Body	1.3 E-6	1.1 E-6	1.2 E-6	1.1 E-6	1.2 E-6	3.8 E-7	6.8 E-6

*S Values for skin as Source Organ were calculated by the reciprocity theorem.
**Maximal value-assuming that all radiations are totally absorbed.

TABLE 2 S, Absorbed Dose Per Unit Cumulated Activity (Rad/μCi-h) for Pt-195m.

Organ	$\tilde{A}$ (μCi-h/μCi administered)
Kidney	3.85
Liver	4.22
Lung	0.41
Spleen	0.21
Skin	16.20
Blood	3.67
Fat	0.89
Muscles	6.94
Marrow	0.25
Bone	5.95
Adrenals	0.18
Brain	0.43
Heart	0.79
Pancreas	0.15
Stomach	0.24
Thyroid	0.15
Testes	0.14

TABLE 3 Cumulated Activities $\tilde{A}$ (μCi-h/μCi administered) for control rats

Organ	Dose (Rad/μCi-administered)
Kidney	4.4×10^{-3}
Liver	1.0×10^{-3}
Lung	2.0×10^{-4}
Spleen	5.5×10^{-4}
Skin	3.4×10^{-3}
Uterus*	1.6×10^{-5}
Whole Body	9.4×10^{-5}

*Not including self dose

TABLE 4 Calculated cumulated doses in reference man per unit activity of Platinum-195m *cis*-dichlorodiammine administered.