Bull. Environm. Contam. Toxicol. 29, 434–439 (1982)

Tissue Distribution and Elimination of Photomirex in Squirrel Monkeys

I. Chu, D. C. Villeneuve, and A. Viau

Environmental and Occupational Toxicology Division, Bureau of Chemical Hazards, Environmental Health Directorate, Ottawa, Ontario K1A 0L2 Canada

Photomirex (8-monohydromirex) residues have been found in soil (CARLSON et al. 1976) and wildlife samples (HALLETT et al. 1976). These residues are most likely due to the degradation of the parent compound mirex which has been used both as an insecticide and a fire retardant. Previous work in our laboratories showed that photomirex when fed to rats caused biochemical changes, reproductive impairment, and histological changes in the liver, thyroid and testes (VILLENEUVE et al. 1979a and b; CHU et al. 1981a). The histological changes in the liver and thyroid persisted long after exposure had terminated (CHU et al. 1981b). In a pharmacokinetic study it was shown that photomirex was retained in the liver and adipose tissue of rats for a prolonged period of time (CHU et al. 1979). Prompted by these findings the present study was carried out as part of our general program on photomirex toxicity and was designed to investigate the pharmacokinetic behavior of photomirex in squirrel monkeys.

MATERIALS AND METHODS

^{14}C-Photomirex used in the study was synthesized according to a procedure previously described (CHU et al. 1979). The specific activity and radiochemical purity of the compound were 1.05 uCi/mg and 96% respectively. The impurities consisted of 3% mirex and 1% dihydromirex. Gas chromatographic (GC) analysis was performed in a Hewlett Packard instrument model 5820A equipped with a Nickel-63 electron capture detector. Gas chromatography-mass spectrometry (GC-MS) analysis was carried out in a Finnigan instrument, model 4000, data system 6000. Conditions for GC and GC-MS analysis are described elsewhere (CHU et al. 1979).

Three squirrel monkeys weighing 677 (No. 1), 875 (No. 2) and 989 (No. 3) g were anesthetized with halothane and cannulated in their jugular veins. Three days after cannulation these animals were given via the cannula single doses of ^{14}C-photomirex (20 mg/kg, 20 uCi) dissolved in Emulphor/ethanol/saline (1:1:8) followed by a saline flush (2 ml). Emulphor (Domtar Canada) is a polyethoxylated vegetable oil used for dissolving lipophilic compounds in water. Serial blood samples (0.3 ml) were withdrawn from the cannula for the estimation of radioactivity. The monkeys were housed in individual metabolism cages with free

0007-4861/82/0029-0434 $01.20

access to water and food for 16, 34 and 52 weeks respectively. Separate collections of urine and feces were made daily until the animals were killed. At necropsy the monkeys were anesthetized with halothane and exsanguinated via the abdominal aorta. Tissues were excised for the estimation of radioactivity. Quantitative and qualitative analysis of the radioactive contents in urine, feces and tissues was carried out using a method previously described (CHU et al. 1979).

RESULTS

Tissue distribution of photomirex after intravenous administration is shown in Table 1. The highest concentrations were found in fat followed by skin, pancreas, adrenals, liver and nerves. Because of the large tissue mass, fat, skin, liver and muscle also served as major storage sites. Redistribution of radioactivity occurred between 16 and 34 weeks after administration, i.e. the muscle and skeleton accounted for 32% of the administered dose in monkey No. 1 (16 weeks) but only 4.1% of the dose in monkey No. 2 (34 weeks). In monkey No. 2 most of the radioactivity was found in the skin and subcutaneous fat.

Analysis of blood for photomirex showed that the blood concentrations, when plotted against time on semilogarithmic paper, could be expressed by a sum of five exponentials (equation below):

$$C_t = A\,e^{-at} + B\,e^{-bt} + C\,e^{-ct} + D\,e^{-dt} + E\,e^{-et}$$

Where C_t and t denote concentration and time respectively. A,B,C,D, and E and a,b,c,d and e represent pool sizes and rate constants respectively (t1/2 = 0.693/rate constant). Crude graphic estimates were made for the parameters A,B,C,D,E, a,b,c,d and e using the method of residuals (also known as feathering method). The data were then analyzed separately for each monkey using a BMDP nonlinear regression program (DIXON 1975) in an HP-3000 computer. The computer derived values are presented in Table 2. Analysis of fecal data in a similar manner indicated that elimination of photomirex conformed to a single exponential term. The decay rate constants for monkey No. 1, 2 and 3 were 0.0052, 0.0039 and 0.0034 (day^{-1}) respectively. Cumulative excretion of photomirex in feces ranged from 5.9-10.3% of the total dose. Urine data were not included in the excretion estimates since urine only contained insignificant amounts of radioactivity.

Radioactive materials present in fat, skin, liver and feces were extracted and purified by a thin-layer chromatographic technique. The GC and GC-MS analysis showed that the radioactive materials found were unchanged photomirex. No metabolites were detected.

Table 1. Tissue distribution of Photomirex (A) ppm (B) percentage of total dose

	Monkey No. 1 (16 wk)		Monkey No. 2 (34 wk)		Monkey No. 3 (52 wk)	
	A	B	A	B	A	B
Perirenal Fat	89	8.1	61	7.8	79	12
Skin and subcutaneous fat	11	12	60	71	36	42
Pancreas	82	2.9	52	.61	54	0.93
Adrenals	17	0.03	9.8	0.014	14	0.02
Liver	19	2.1	11	1.1	10	1.8
Kidneys	1.4	0.03	0.95	0.021	1.4	0.038
Spleen	0.6	0.003	1.8	0.005	1.1	0.009
Cerebrum	1.6	0.19	1.4	0.16	1.2	0.21
Cerebellum	1.2	-	1.0	0.013	1.2	0.02
Heart	1.6	0.028	1.4	0.028	1.3	0.031
Lungs	0.66	0.017	0.76	0.027	0.90	0.021
Testes	1.5	0.017	1.4	0.020	0.68	0.006
Intestines	3.6	0.09	3.5	0.13	6.5	0.15
Urinary Bladder	1.8	0.006	1.3	0.002	2.2	0.007
Thyroids	-	-	-	-	5.4	0.003
Salivary Glands	-	-	1.4	-	2.2	-
Spinal Cord	1.9	-	2.8	-	1.8	-
Sciatic Nerve	24	-	4.7	-	9.4	-
Eyes	0.7	0.014	0.3	0.004	0.42	0.01
Muscle and bone	1.5	32.0	1.3	4.1	0.3	9.8
Gastrointestinal Content	2.6	0.46	2.0	0.28	-	0.036
Feces	-	5.9	-	7.6	-	10.3

Table 2. Kinetic parameters of elimination of photomirex from blood after i.v. administration and curve-fitting to the equation $C_t = A\,e^{-at} + B\,e^{-bt} + C\,e^{-ct} + D\,e^{-dt} + E\,e^{-et}$

	Pool Size (ug/kg)					Elimination Rate Constant (day^{-1})				
Monkey	A	B	C	D	E	a	b	c	d	e
No. 1 (16 wk)	83	15.3	1.53	0.28	0.079	1412	159	2.46	0.38	0.0046
No. 2 (34 wk)	85	10.6	3.35	0.46	0.20	282	54	1.73	0.13	0.00057
No. 3 (52 wk)	84	9.0	5.58	0.92	0.16	308	56	4.09	0.39	0.0012

[1] t1/2 = 0.693/elimination rate constant (day^{-1}).

DISCUSSION

The results of the present study are in general agreement with those of our previous work on photomirex and 2,8-dihydromirex in rodents (CHU et al. 1979, 1980). After intravenous administration of ^{14}C-photomirex to squirrel monkeys radioactivity rapidly disappeared from the blood with very little being excreted in the feces and urine, suggesting an extensive tissue uptake of the compound. Redistribution of photomirex resulted in a higher concentration in the fatty tissues. All of these features were also observed in rats (CHU et al., 1979). However, we observed a difference in the rate of fecal elimination between monkeys and rats which could be important in selecting an appropriate animal model for the extrapolation of this type of data to humans. Approximately 10.3% of the administered dose was eliminated in monkey feces over a one-year period compared with 51-55% excreted in rat feces in 28 days (CHU et al., 1979). In the present study the concentration of photomirex in fat was decreased by 11% in a 36-week period (from 89 ppm for 16 weeks to 79 ppm for 52 weeks). In contrast the concentration of photomirex in the same tissues of rats was reduced to 25% of the initial concentration in 21 days.

The rate constants and pool sizes given in Table 1 are quite similar for monkey No 2 and 3, but not No. 1. The differences could be due to the length of time in which the blood concentrations were monitored. In monkey No. 1 the period is probably not long enough to permit a proper estimate of a slow-excreting chemical like photomirex. In addition redistribution which occurred after 16 weeks may also have contributed to the observed differences. In our study we found that a sum of 5 exponentials was a better fit for the decay of photomirex in monkey blood. This result agreed with that of PITTMAN et al. (1976) who suggeted that the blood concentration curve of mirex consisted of at least more than four linear components. YANG et al. (1978) reported that after an intravenous dose of ^{14}C-hexachlorobenzene to rhesus monkeys cumulative fecal and urinary excretion in one year accounted for 28.2 and 1.6% of the dose. Compared to HCB, photomirex has a very long half-life in primates and may be one of the most slowly-eliminated chemicals ever examined.

Acknowledgements

The authors thank Mr. D. Biggs for statistical analysis, L. Martin for technical assistance and Mrs. J. Ireland for typing the manuscript.

REFERENCES

CARLSON, D.D., D.A. KANYHA, W.B. WHEELER, G.P. MARSHALL and R.G. ZAYLSKIE: Science 194, 939 (1976).

CHU, I., D.C. VILLENEUVE, V. SECOURS, G.C. BECKING, A. VIAU and F.M. BENOIT: Drug Metab. Dispos. 7, 24 (1979).

CHU, I., D.C. VILLENEUVE, G.C. BECKING, and A. VIAU: J. Toxicol. Environ. Hlth. 4, 713 (1980).
CHU, I., D.C. VILLENEUVE, V.E. SECOURS, V.E. VALLI, and G.C. BECKING: Toxicol. Appl. Pharmacol. 60, 549 (1981a).
CHU, I., D.C. VILLENEUVE, B.L. MACDONALD, V.E. SECOURS and V.E. VALLI: Toxicology, 21, 235 (1981b).
DIXON, W.J.: Nonelinear Regression in BMDP, pp. 541-572. Berkeley, Univ. of California Press (1975).
HALLETT, D.J., R.J. NORSTROM, F.I. ONUSKA, M.W. COMBA, and R. SAMPSON: J. Agr. Food Chem. 24, 1189 (1976).
PITTMAN, K.A., W. WIENER, and D.H. TREBLE: Drug Metab. Dispos. 4, 288 (1976).
VILLENEUVE, D.C., L. RITTER, G. FELSKY, R.J. NORSTROM, I.A. MARINO, V.E. VALLI, I. CHU and G.C. BECKING: Toxicol. Appl. Pharmacol. 47, 105 (1979a).
VILLENEUVE, D.C., V.E. VALLI, I. CHU, V. SECOURS, L. RITTER and G.C. BECKING: Toxicology 12, 235 (1979b).
YANG, R.S.H., K.A. PITTMAN, D.R. ROURKE, V.B. STEIN: J. Agric. Food Chem. 26, 1076 (1978).

Accepted August 23, 1982