

COMPARISON OF THE CONCENTRATION IN MALIGNANT MELANOMAS OF ¹²⁵I FROM 6-IODO- VERSUS 7-IODO-4-(3-DIMETHYL- AMINOPROPYLAMINO) IODOQUINOLINE

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We have reported that an iodinated analog of chloroquine (NM-113), 4-(3-dimethylaminopropylamino)-7-iodoquinoline-¹²⁵I (hereafter referred to as the 7-iodoisomer) concentrates in malignant melanoma relative to other tissues similar to the concentration of ¹⁴C from chloroquine (1). This target-to-nontarget concentration was sufficient in mice, hamsters and humans with melanomas to allow diagnostic scanning (2).

The isomer of this compound with radioiodine at the 6-position was synthesized* and evaluated under identical conditions in mice and hamsters with malignant melanomas to determine how the difference in structure would affect the concentration of this compound in melanin-containing tissues. We report here that the radioactivity tissue distribution after the 6-iodo analog was similar to that after the 7-iodoisomer.

METHODS

Twelve mice of the C57B1/6J strain (black) with B-16 melanomas, 3-5 weeks of age and weighing approximately 15-30 gm, were injected i.p. with 10 μ Ci of the 6-iodoisomer. Four Syrian hamsters with transplanted melanomas (1) were injected with 100 μ Ci of the 6-iodoisomer.

Twenty-four, 48, 72 and 96 hr after injection, three mice (at each time interval) were anesthetized and sacrificed and representative 50-mg samples were obtained from melanoma and 15 other tissues as shown in Table 1 and as described previously (1). The hamsters were killed at 4 and 6 days as shown in Table 2, and similar tissue samples were taken. The samples were counted in a commercial well counter with corrections made for decay. The result-

ing data are compared with our data previously reported for the 7-iodo derivative (1) with a similar specific activity (10-20 μ Ci/mg).

The 7-iodo compound was prepared according to methods reported previously (3).

RESULTS

Table 1 compares the distribution of radioactivity in mice following the administration of the 6-iodoisomer with our previous data on the 7-iodoisomer. Although the radioactivity concentration is considerably higher in mice after the 7-iodo than after the 6-iodoisomer in equivalent doses, the relative distribution of radioactivity concentration in each tissue is comparable at each time interval.

Table 2 compares the tissue distribution of the 6-iodo and the 7-iodoisomer in hamsters. The radioactivity concentration is higher in the three hamsters at 6 days after the 6-iodoisomer than in one hamster at 4 days, but the relative distribution of radioactivity concentration in each tissue is comparable at each time interval. The concentration in melanoma in mice after both isomers was highest at 24 hr and then fell with time. The concentration ratio in eyes-to-melanoma was approximately 3:1 at Day 1, 4:1 at Day 2, 4.5:1 at Day 3 and 3.5:1 at Day 4. The melanoma-to-liver ratio was 1.1:1 at Day 1, 4.5:1 at Day 2, 6.5:1 at Day 3 and 7:1 at Day 4. The thyroid-to-melanoma ratio (presumably from some de-iodination) was 4.3:1 at Day 1, 19:1 at Day 2, 10:1 at Day 3 and 6.5:1 at Day 4. There was no significant difference between these ratios after the 6-iodoisomer and the 7-iodoisomer. No explanation is ap-

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TABLE 1. DISTRIBUTION OF RADIOACTIVITY FOLLOWING ADMINISTRATON OF ¹²⁵I-6-IODO NM-113

No. of mice	Avg. wt. of mice (gm)	NM-113 (mg)	Time (hr after injection)	Melano- ma	Eye	Skin	Liver	Kidney	Muscle	Blood
¹²⁵I-6-Iodo NM-113										
3	22	1.02	24	57.0 ±21.7	178.0 ±43.5	26.5 ±7.8	49.6 ±15.4	20.1 ±9.1	13.0 ±7.1	1.4 ±0.2
3	21	1.02	48	26.5 ±4.3	109.6 ±30.0	20.0 ±4.3	6.0 ±0.7	2.3 ±0.4	0.5 ±0.2	0.2 ±0
3	24.3	1.19	72	25.7 ±0.6	115.9 ±7.7	21.0 ±1.7	4.3 ±0.2	1.7 ±0.1	1.0 ±0.5	0.1 ±0.03
3	25	1.19	96	20.7 ±10.8	73.8 ±3.8	18.4 ±2.7	3.2 ±0.3	0.85 ±0.1	0.7 ±0.2	0.1 ±0.04
¹²⁵I-7-Iodo NM-113										
3	19.3	1.1	24	315.3 ±21.3	499.0 ±46.6	154.3 ±5.6	132.7 ±9.4	79.7 ±11.7	27.4 ±4.5	28.1 ±3.5
3	19.7	1.1	48	156.7 ±45.3	555.1 ±507.2	136.8 ±10.4	39.6 ±1.7	31.0 ±15.5	13.5 ±20.0	11.1 ±1.6
3	17.3	1.1	72	186.6 ±27.5	582.5 ±98.7	196.9 ±9.2	28.3 ±7.9	17.6 ±5.2	4.9 ±1.4	5.2 ±0.8
3	17.0	1.1	96	84.7 ±24.0	545.1 ±178.3	166.6 ±55.7	10.1 ±3.0	4.9 ±1.4	11.3 ±7.3	1.8 ±1.0

* Cpm/mg ± SEM; dose ¹²⁵I = 10 μCi.

TABLE 2. DISTRIBUTION OF RADIOACTIVITY FOLLOWING ADMINISTRATON OF ¹²⁵I-6-IODO NM-113

No. of ham- sters	Wt. of hamster (gm)	NM-113 (mg)	Time (days after injection)	Melano- ma	Eye	Skin	Liver	Kidney	Muscle	
¹²⁵I-6-Iodo NM-113 (cpm/mg ± SEM)										
1	143	12.3	4	53.0	77.4	40.9	40.6	30.8	2.5	
3	147	8.55	6	93.5 ±11.1	164.1 ±32.2	108.6 ±31.07	25.8 ±10.2	23.0 ±8.9	2.9 ±0.16	
¹²⁵I-7-Iodo NM-113 (cpm/mg)										
1	158	5.3	4	102.3	295.2	4.5	48.6	62.4	5.4	
1	162	4.8	6	69.2	244.5	55.2	25.9	121.4	2.4	

* Dose ¹²⁵I = 100 μCi.
† Thyroid blocked with Lugol's solution.

parent for the increased radioactivity concentration in tissues after the 7-iodoisomer compared to the 6-iodoisomer in mice at all time intervals.

DISCUSSION

These data on two chloroquine analogs, one radioiodinated at the 6- position and the other at the 7- position, indicate that relative tissue binding is independent of the location of the iodine on the molecule. The explanation for the higher tissue-radioactivity concentration in almost all tissues after the administration of the 7-iodoisomer in mice is not certain. It is theoretically possible that batches of either compound with a higher specific activity would result in generally higher radioactivity concentration

in all tissues. We did not check the manufacturer's assay of the specific activity of each compound in our own laboratory. If such difference in specific activity existed, it did not appear to cause a difference in the relative tissue binding of the two compounds.

Wiselogle (4) has presented data to show that the antimalarial activity of chloroquine halogenated at the 7- position is seven times greater than at the 6- position, 25 times greater than at the 5- position and over 75 times greater than at the 8- position.

O'Brien and Hahn (5) reported that there was no difference in the antimalarial activity of the two isomers considered here, but marked diminution of effect with other position substitutions. The present data therefore do not settle the question of whether

COMPARISON OF COMPOUND CONCENTRATION IN MALIGNANT MELANOMAS

AND ¹²⁵I-7-IODO NM-113 IN PIGMENTED MICE WITH MELANOMAS*

Adrenal	Spleen	Lung	Thyroid	Bladder	Heart	Intestine	Fat	Brain	Pancreas	Sternum
¹²⁵ I-6-iodo NM-113										
62.7	123.0	59.3	245.5	79.3	41.1	65.7		27.5	33.7	14.5
±18.8	±46.3	±21.2	±106.9	±24.6	±32.9	±22.0		±14.9	±20.6	±5.4
86.0	9.9	5.9	516.3	17.9	0.5	1.5		14.0	2.1	1.0
±49.6	±4.5	±1.6	±355.7	±6.2	±0.1	±0.3		±7.9	±0.5	±0.4
13.2	3.7	3.8	251.0	17.7	0.5	2.1	2.8	6.2	2.0	1.1
±1.1	±0.1	±1.0	±51.7	±3.4	±0.04	±0.6	±2.3	±1.8	±0.6	±0.3
7.3	2.6	2.1	136.5	7.8	0.5	2.8		1.9	1.3	1.7
±2.0	±0.8	±0.3	±109.9	±1.2	±0.1	±1.5		±0.3	±0.2	±1.1
¹²⁵ I-7-iodo NM-113										
306.2	174.9	218.2	1,528.7	259.5	34.6	134.7	27.5	80.8	177.7	
±19.2	±34.7	±30.3	±629.4	±38.7	±6.9	±23.7	±2.0	±1.8	±22.6	
193.3	45.4	46.9	2,532.5	180.3	13.8	78.6	47.3	22.1	64.2	
±349.1	±6.6	±6.2	±3,215.8	±101.7	±0.05	±75.5	±18.2	±5.0	±5.0	
192.2	74.6	41.0	2,295.8	84.6	5.4	34.7	71.7	15.4	46.4	
±43.7	±35.5	±10.4	±985.9	±22.8	±1.6	±8.2	±19.8	±7.5	±15.9	
118.6	12.1	9.7	2,742.2	22.2	5.1	20.5	25.2	6.6	17.4	
±28.6	±7.0	±4.5	±1,790.8	±10.6	±2.7	±13.2	±22.3	±1.7	±12.1	

AND ¹²⁵I-7-IODO NM-113 IN SYRIAN HAMSTERS WITH MELANOMAS*

Blood	Adrenal	Spleen	Lung	Thyroid	Bladder	Heart	Intestine	Fat	Pancreas
¹²⁵ I-6-iodo NM-113 (cpm/mg ± SEM)									
—	41.2	12.5	2.4	15.5†	19.3	2.3	—	2.0	13.6
1.78	43.5	17.2	9.2	305.5	5.1	2.1	4.0	1.9	70.2
±0.83	±15.1	±5.4	±1.4	±199.0	±0.6	±0.07	±0.7	±0.71	±23.6
¹²⁵ I-7-iodo NM-113 (cpm/mg)									
1.0	46.0	47.8	19.1	2,142.7	110.4	2.7	43.6	8.9	—
0.5	24.8	20.5	7.6	—	25.5	1.2	6.1	31.8	—

or not binding of these chloroquine analogs to melanin-containing tissues is related to the position of the iodine atom on the molecule or related to the antimalarial activity of chloroquine. The data do indicate, however, that the clinical utility of the 6-iodo compound should not differ from that of the 7-iodo compound.

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