Detection of Ocular Melanoma with 4-(3-Dimethylaminopropylamino)-7-[^{123}I]-Iodoquinoline

Richard M. Lambrecht, Samuel Packer, Alfred P. Wolf, David Lloyd, and Harold L. Atkins

Brookhaven National Laboratory, Upton, North Shore University Hospital, Manhasset, Cornell University Medical School, New York, and State University of New York, Stony Brook, New York

Iodine-123-labeled 4-(3-dimethylpropylamino)-7-iodoquinoline was evaluated in nine patients. By using a specially designed dual-pinhole ocular collimator, it was possible to obtain positive images at 2–6 hr for only 70% of the cases with subsequently proven ocular melanomas.

J Nucl Med 25: 800–804, 1984

No single radiopharmaceutical, or therapeutic modality, or combination of them, has proven very effective in diagnosis or treatment of disseminated malignant melanoma. Several chloroquine analogs labeled with I-125 or I-131 have been tested in animal models (*1–6*). In patients, the detection of skin or ocular melanoma with iodinated quinolines has met with limited success (*7–14*). This class of compounds was chosen because of a known melanotropic affinity and selective localization in the pigmented structures of the eye (*15,16*). Beierwaltes and colleagues (*7,9*) achieved encouraging results with 4-(3-dimethylpropylamino)-7-[^{125}I]iodoquinoline. Two limitations were the physical properties of I-125 ($T_{1/2}$ = 60.2 d, γ = 35.5 keV), and the lack of satisfactory detection instrumentation.

Blanquet and co-workers were first successful in imaging the eyes of man with ocular tumors: they utilized a gamma camera with a modified dual-pinhole collimator and a poorly characterized I-131-labeled quinoline analog (*11–13*).

We have used high-purity I-123 and are summarizing our experiences with 4-(3-dimethylpropylamino)-7-[^{123}I]iodoquinoline administered to nine patients having confirmed ocular melanoma (*3*).

METHODS

Radiopharmaceutical preparation. Iodine-123, containing 0.8 ± 0.1% I-124 at time of use, was recovered as iodide by the previously described methods (*17*). The $^{123}I^-$ was transferred into a reaction ampoule containing 20 μl of a 50 mg/ml solution of nonradioactive 4-(3-dimethylpropylamino)-7-iodoquinoline in conc. H_3PO_4. The reaction vessel was flushed with N_2, evacuated, and sealed, then immersed in an oil bath at 190–200°C for a nominal 0.5 hr. The contents were transferred with 0.3 ml of sterile H_2O to a centrifuge tube. Sodium hydroxide (6.25 *M*, 125 μl) was added and the contents were extracted twice with $CHCl_3$. The extracts were filtered through glass wool and anhydrous Na_2SO_4. Ten μl of the $CHCl_3$ solution was used for quality control, and the remainder was evaporated with N_2. The preparation was dissolved with 50 μl of 0.1 *M* HCl, and 4 ml of isotonic saline, USP 0.9%) were added. The pH ranged from 4 to 7. The solution was filtered through a 0.22-μ Millipore into a multi-injection vial and autoclaved at 121°C for 20 min. The specific activity of all preparations, which were administered within 2 hr of formulation, was 0.10 ± 0.03 mCi/mg.

The P-32 uptake test was made 48 hr after administration of sodium[^{32}P]phosphate.*

Quality control. The radiochemical purity of the final product was monitored by thin-layer chromatography (TLC) on silica gel using 20:20:1; methylene chloride/acetonitrile/triethylamine. Hydrazine (0.05%) was used to retard air oxidation. The TLC strip was air-dried, immediately covered with cellophane, sectioned, and assayed in a scintillation well counter. The R_f of I-123-4-(3-dimethylpropylamino)-7-[^{123}I]iodoquinoline was 0.40. Radioiodide appeared at the solvent front, and was <0.5% of the total activity. Alternate TLC systems

Received Dec. 29, 1983; revision accepted Mar. 28, 1984.

For reprints contact: Samuel Packer, MD, Medical Research Center, Brookhaven National Laboratory, Upton, NY 11973.

TABLE 1. IN VITRO DISTRIBUTION AND UPTAKE OF 4-(3-DIMETHYLAMINOPROPYLAMINO)-7-[^{125}I]IODOQUINOLINE IN A PATIENT'S EYE AT 20 hr AFTER POST-ORAL ADMINISTRATION*

Tissue	Relative distribution†	Uptake (%/g)‡
Melanoma (cell type: mixed)	1.00	~0.02
Choroid	0.58	
Retina	0.39	
Cornea	0.51	
Lens	0.55	
Iris	0.44	
Sclera	0.45	

* The oral preparation was prepared by converting the radiopharmaceutical to its bichloride to make it soluble in 100 ml of orange-flavored water containing 85 g of sucrose.

† Based on %/g wet weight of tissue.

‡ Percent of injected dose per gram of tumor. Total detailed dissection of individual component structures was not possible. Roughly 20–50% of each structure other than tumor was assayed.

are n-butanol/acetic acid/water (6:15:2.5), $R_f = 0.45$; and methanol/triethylamine (40:1), $R_f = 0.57$.

The radionuclide purity was determined with a GeLi detector and found to range around 0.8 ± 0.1% for all preparations at the time of use.

The 4-(3-dimethylpropylamino)-7-iodoquinoline was synthesized by the method of Counsell et al. (*18*). Chemical identity and purity were confirmed by agreement with reported analytical data. Production samples were routinely sent to an independent laboratory for sterility and apyrogenicity testing.

Patient selection. The patients were selected, with proper consent, on the basis of standard ophthalmologic examinations. The decision to enucleate a patient's eye was based solely on the results of standard ophthalmic diagnostic modalities, including the P-32 uptake test. Oral administration was used for only the first patient, in order to confirm uptake of the radiopharmaceutical in the ocular melanoma of a patient previously scheduled for enucleation. The tracer was administered i.v. to all other patients.

INSTRUMENTATION

A gamma camera equipped with a specially fabricated dual-pinhole collimator, provided with a restraining strap to hold the patient's head in a stationary position, was used for imaging (*19*). The P-32 uptake test was determined with a semiconductor eye probe.

RESULTS AND DISCUSSION

The first study was performed to compare the relative distribution of I-123 in the human eye, compared with the results obtained for the Greene melanoma in the Syrian hamster (*3*). The patient received an oral dose of 0.57 mCi of the radiopharmaceutical 20 hr before the scheduled enucleation. The excised eye was dissected and the various structures assayed for radioactivity as summarized in Table 1. The tumor-to-choroid ratio was nearly 2:1. Uptake by the tumor was 0.02% dose/g. The result was similar to the uptake in the animal model, and was also comparable (*20*) to P-32 uptake data obtained in humans.

The required dose for a successful image was 4.5 mCi. This corresponded to a chemical dose of 40–50 mg, which is 5–20% of the daily dose of chloroquine when it is used as an antimalarial. The estimated absorbed radiation doses (rad/5.0 mCi) for a preparation containing <0.8% I-124 as the major radionuclidic impurity were: thyroid 2.23 (assuming 3.6% of the radioiodine went to the organ), gonads 0.08, liver 0.03, eye with melanoma 0.05, and whole body 0.29. The average dose estimates to the organs are based upon distribution data obtained by i.p. administration to the Syrian hamster and calculated using the MIRD scheme.

Figure 1 presents typical scintigrams of a patient's eyes at 2 and 6 hr after i.v. administration. At 2 hr the

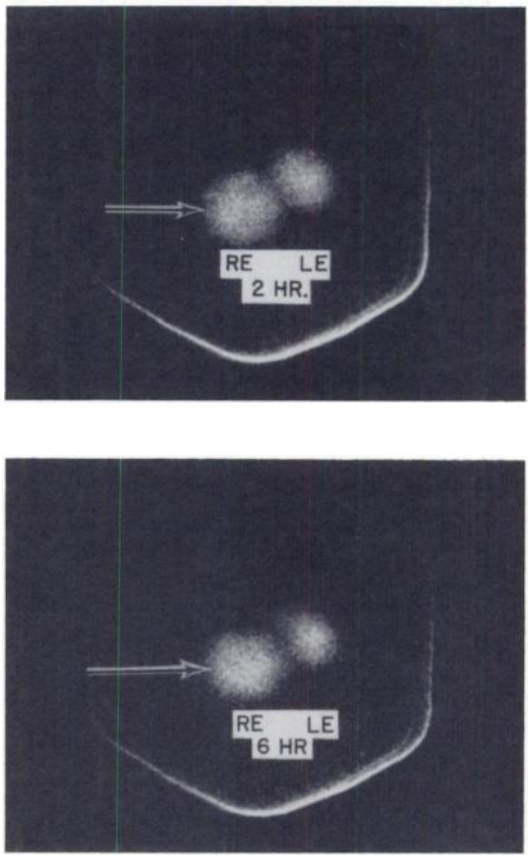

FIG. 1. Scintigrams obtained with dual-pinhole collimator following i.v. administration of 4.5 mCi of I-123 4-(3-dimethylpropylamino)-7-[I-123]iodoquinoline to patient with ocular melanoma (arrow). RE and LE refer to right and left eye, respectively.

TABLE 2. DOUBLE-PINHOLE-COLLIMATOR IMAGES WITH 4-(3-DIMETHYLAMINOPROPYLAMINO)-7-[^{123}I]-IODOQUINOLINE AND P-32 UPTAKES IN PATIENTS WITH OCULAR MELANOMA

Patient	Image	P-32 uptake†	Tumor size (mm)	(mm^3)	Cell type
MR	+	241	7.5 × 7.5 × 5	280	Epithelioid
LZ	+	381	12 × 14 × 6	840	Epithelioid
MG	-	81	15 × 15 × 5	1125	Mixed
JM	+	364	16 × 16 × 6	1176	*
JL	+	235	12 × 12 × 6	864	*
JW	+	195	11 × 11 × 4	484	*
AD	-	400	14 × 16 × 10	2240	*
EE	-	140	16 × 16 × 8	1568	*

* Treated with iodine-125 or cobalt-60.
+ All positive.

radioactivity was asymmetric, with more activity in the eye with the tumor. At 6 hr there was a slight reduction in the activity in the normal eye. Dynamic scintigrams of both eyes at the time of injection gave symmetric images. One week later, the patient's eye was enucleated following the positive result of a P-32 uptake test. The tumor cell type was predominantly epithelioid.

Table 2 summarizes the results obtained for eight cases. The images were interpreted as positive if a focus of increased activity was readily discernible. Positive images were obtained for 70% of the histologically confirmed tumors, and only for the smaller tumors. Either tumor necrosis in large tumors, and/or hypervascularization, or an enhanced metabolic incorporation of the iodinated quinoline analog in small tumors, can account for the observations. The mechanism of localization of quinolines in pigmented cells is uncertain. The patient population for this study is too small to establish whether the positive result for small tumors is a general and predictable observation, or is related to the degree of pigmentation. Human mortality from ocular melanoma has been shown to vary with the degree of pigmentation (*21*,*22*). With the limited number of patients studied and the relatively low specific activity used, it was not possible to correlate uptake with the concentration of pigment or the number of binding sites.

The limited case data suggest that the uptake of 4-(3-dimethylpropylamino)-7-[^{123}I]iodoquinoline is marginal, and that the background is too intense to permit routine imaging of ocular tumors. The high background is due in part to the high uptake by the brain. The results of Fig. 2 were obtained with the gamma camera and a medium-energy collimator. The uptakes by the brain, anterior vascular regions, and the cavernous

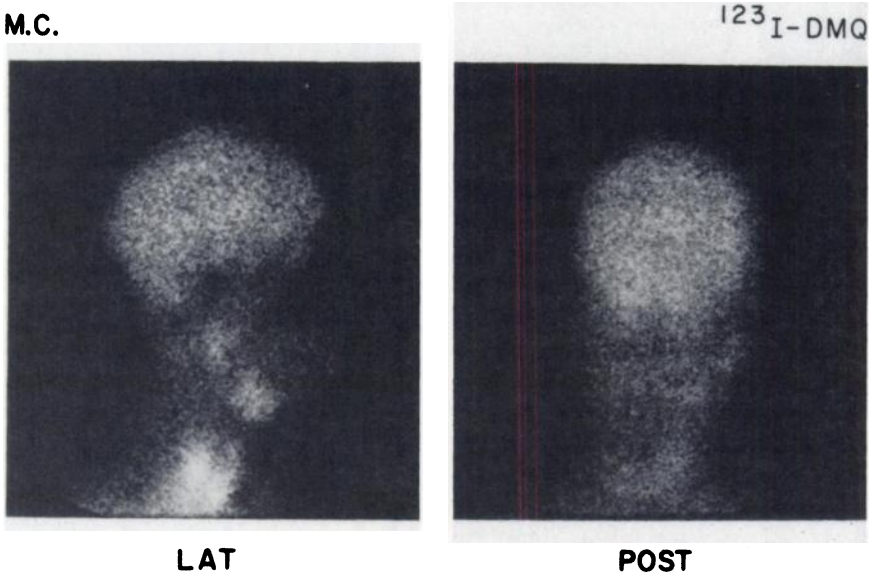

FIG. 2. Brain scintigrams of patient at 6 hr after i.v. administration of 5 mCi of I-123 4-(3-dimethylpropylamino)-7-[I-123]iodoquinoline.

sinuses require the use of the special dual-pinhole collimator in order to obtain a "positive" ocular image.

The efficacy for detection of choroidal melanoma with the radiopharmaceutical and special instrumentation was comparable to the usual success for imaging malignant melanoma (*24*). In another study limited to Ga-67 citrate, we (*24*) obtained comparable efficacy (seven of 11 patients) when using a differential radioactivity monitor for simultaneously counting the Ga-67 radioactivity in each eye. We have not been able to study both the Ga-67 and I-123 radiopharmaceuticals in the same patient, but we conclude that 4-(3-dimethylpropylamino)-7-[^{123}I]iodoquinoline does not appear to offer sufficient advantages over Ga-67 to merit a recommendation for its routine diagnostic use. The effort and expense that 4-(3-dimethylpropylamino)-7-[^{123}I]iodoquinoline involves are also drawbacks. Possibly emission tomography would aid in distinguishing the ocular from brain radioactivity.

We suggest that the C-13-labeled compound merits exploration for imaging with NMR. This would eliminate the high radiation dose (*25*) to the patient, and result in images with higher resolution if the uptake is sufficient. The background activity resulting from 4-(3-dimethylpropylamino)-7-[^{123}I]iodoquinoline, administered orally, decreased after a period of several days (*2*). Ocular melanoma is a slowly growing cancer, so that specificity might be higher if the patient receives the C-13 compound over a period of a week or more and imaging is attempted much later.

Obtaining confirmatory data on a patient population is very slow, due to the limited number of cases and the time course of diagnosis, treatment, and eventual—if necessary—enucleation.

FOOTNOTE

* Squibb.

ACKNOWLEDGMENTS

This research was supported by the U.S. Department of Energy and its Office of Health and Environmental Research. Partial support was obtained from NCI Grant No. CA24597, and a grant from the Kirsten Foundation. Stimulating discussions with Professor P. Blanquet concerning his experience with ocular melanoma are acknowledged with appreciation. Mr. Kulberg, of Siemans, Amsterdam, kindly provided the set of tungsten stenopeic apertures used in the dual-pinhole collimator.

REFERENCES

1. BEIERWALTES WH, VARMA VM, LIEBERMAN LM, et al: Scintillation scanning of malignant melanomas with radioiodinated quinoline derivatives. *J Lab Clin Med* 72: 485-494, 1968
2. BEIERWALTES WH, VARMA VM, COUNSELL RE, et al: Scintillation scanning of malignant melanomas with radioiodinated quinoline derivatives. *J Nucl Med* 9:489-491, 1968
3. PACKER S, REDVANLY CS, LAMBRECHT RM, et al: Quinoline analog labeled with iodine 123 in melanoma detection. *Arch Ophthalmol* 93:504-508, 1975
4. GOULDING RW, DANPURE HJ, SOMAIA S, et al: Radioiodine labelled 4-amino-7-iodoquinolines for melanoma detection. *J Label Cmpd Radiopharm* 16:46-48, 1979
5. BUBECK B, EISENHUT M, HEIMKE U, et al: Melanoma affine radiopharmaceuticals I. A comparative study of ^{131}I-labeled quinoline and tyrosine derivatives. *Eur J Nucl Med* 6:227-233, 1981
6. BOCKSLAFF H, KLOSTER G, SAFI N, et al: L-3-^{123}iodo-α-methyltyrosine or 6-^{123}iodochloroquine as imaging agents for the detection of malignant melanoma: A comparative study on tumor bearing Syrian golden hamsters. *Radioakt Isot Klin Forsch* 14:171-178, 1980
7. BOYD CM, BEIERWALTES WH, LIEBERMAN LM, et al: ^{125}I-labeled chloroquine analog in the diagnosis of ocular melanomas. *J Nucl Med* 12:601-605, 1971
8. VERIN P, BLANQUET P, SAFI N, et al: Nouvelles applications des isotopes dans le diagnostic ophthalmologique. *Bull Soc Ophthalmol Fr* 70:640-648, 1970
9. KNOLL GF, LIEBERMAN LM, NISHIYAMA H, et al: A gamma ray probe for the detection of ocular melanomas. *IEEE Nucl Sci* NS-19:76-80, 1972
10. PAUWELS EKJ, VAN LANGEVELDE A, KASPERSEN FM, et al: Non-invasive detection of ocular melanoma: A patient study with ^{67}Ga- and ^{99m}Tc-citrate and animal studies with a iodoquinoline analogue. *Nucl Med Comm* 1:224-232, 1980
11. SAFI N, BLANQUET P, VERIN PH: La Scintigraphic Oculaire. In *Medical Radioisotope Scintigraphy*, Vol. 2, IAEA, Vienna, 1973, pp 497-518
12. BLANQUET P, VERIN PH, SAFI : La scintigraphic oculaire. In *La Nouvelle Presse Medicale*, Vol. 3, pp 2154-2158, 1974
13. SAFI N, BLANQUET P, BASSE-CATHALINA B, et al: Radionuclidic explorations in ophthalmology. *Int J Nucl Med Biol* 2:166-173, 1975
14. BEIERWALTES WH, LIEBERMAN LM, VARMA VM, et al: Visualizing human malignant melanoma and metastases. Use of chloroquine analog tagged with iodine 125. *JAMA* 206:97-102, 1968
15. POTTS AM: The reaction of uveal pigment in vitro with polycyclic compounds. *Invest Ophthalmol* 3:405-416, 1964
16. BERNSTEIN H, ZVAIFLER N, RUBIN M, et al: The ocular deposition of chloroquine. *Invest Ophthalmol* 2:384-392, 1963
17. LAMBRECHT RM, KONDO K, NORTON E, et al: Cyclotron isotopes and radiopharmaceuticals. XXII. Improved targetry for ^{123}I and ^{124}I production. *Int J Appl Radiat Isot* 28: 765-771, 1977
18. COUNSELL RE, POCHA R, RARADE VV, et al: Tumor localizing agents. VII. Radioiodinated quinoline derivatives. *J Med Chem* 12:232-236 (1969)
19. PACKER S, LAMBRECHT RM, FAIRCHILD RG, et al: Non-invasive detection of choroidal melanoma. In *Intraocular Tumors*. Lomatzsch PK, Blodi FC, eds. Berlin, DDR, Akademe-Verlag, 1983, pp 227-234
20. PACKER S, LANGE R: Radioactive phosphorus for the detection of ocular melanomas. *Arch Ophthalmol* 90:17-20, 1973
21. WILDER HC, PAUL EV: Malignant melanoma of the choroid and ciliary body: A study of 2,535 cases. *Milit Surg* 109: 370-515, 1951
22. SEDDON JM, ALBERT DM, LAVIN PT, et al: A prognostic

factor study of disease—free interval and survival following enucleation for uveal melanoma. *Arch Ophthalmol* 101: 1894–1899, 1983

23. MILDER MS, FRANKEL RS, BUKLEY GB, et al: Gallium-67 scintigraphy in malignant melanoma. *Cancer* 32:1350–1356, 1973

24. LAMBRECHT RM, PACKER S, ATKINS HL: Differential radioactivity monitor for non-invasive detection of ocular melanoma. *Nucl Med Comm:* in press

25. WEINREICH R, BOCKSLAFF H: Radiation doses to the eye lens from ocular tumor seeking radiopharmaceuticals. *Eur J Nucl Med* 8:127–130, 1983

Erratum

In the article entitled, "Lung Clearance Mechanisms in Obstructive Airways Disease," Vol. 25, April 1984, pp. 447-454, Figure 2 was printed incorrectly. It is correct as shown below:

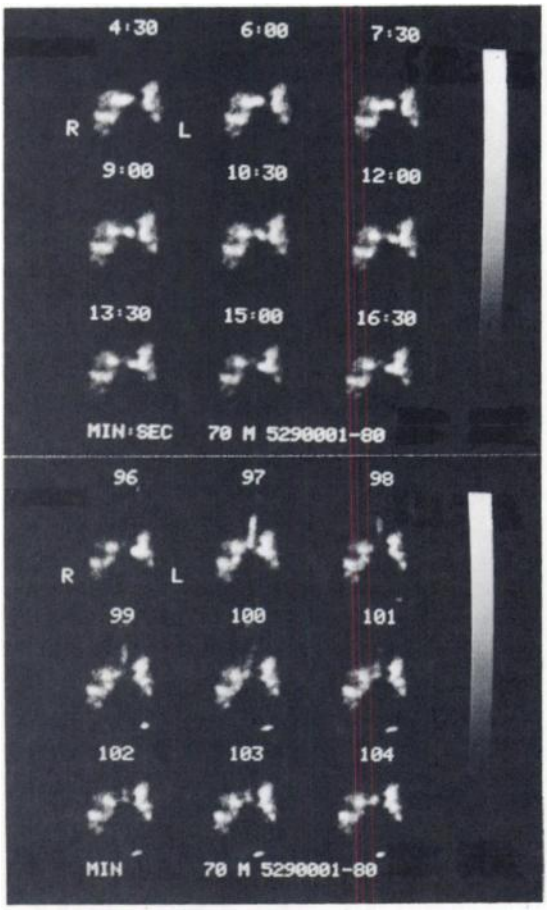

FIG. 2. Top: One-min images, starting from indicated times after radioaerosol inhalation (earlier phase), in 70-yr-old man with pulmonary emphysema and history of recurrent infections. Note shot of radioactivity gradually migrating from right bronchus into left. (Right lung is toward viewer's left.) Below left lung is swallowed radioactivity in stomach. Here image color code was normalized to peak activity detected. In actual radioaerosol inhalation lung cinescintigraphy, each 10-sec frame is transformed to cine mode to allow visual evaluation of dynamic mucus transportation and lung clearance. Bottom: Still images (later phase) from same patient. Cough occurred at 97 min, and radioactivity was pushed cephalad. At 98 min some radioactivity was swallowed into stomach where radioactivity again increased. Shuttle motions of radioactivity persisted between right and left bronchi after coughing subsided.