MELANOMA DETECTION WITH RADIOIODOQUINE

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Under favorable circumstances occult malignant melanomas, either primary or metastatic, have been detected with ^{131}I-iodoquine. This compound, an analog of chloroquine, shares with it the property of reversible adsorption to melanin pigment (*1*). It has no special predilection for tumor tissue *per se*, but after systemic administration, it is selectively accumulated in sites of melanin storage including cutaneous pigmented structures, the pigmented tissues of the eye and melanotic tumors. Because this material is used by us only for diagnostic purposes, low levels of administered radioactivity are involved (20–200 μc), and the calculated radiation dose to the lens is two to three orders of magnitude less than the minimum cataractogenic dose. Chronic animal experiments involving doses of from 40 to 1,000 times those which we use clinically have not shown pathological eye changes.

METHOD

In earlier animal experiments (*2*), melanomas were detected by conventional gamma-ray scanning techniques, but preliminary clinical studies suggested that rather large doses would be required to accomplish this in patients. We have therefore chosen to count over selected regions of the patient and compare the radioactivity in anatomically symmetric sites—for example, the axillae, groins and lung fields. This technique has been somewhat more tedious, but affords a greater sensitivity and hence involves a lower dose of radioactivity to the patient.

The technique that we have found most suitable to date has been to administer the ^{131}I-iodoquine* intravenously approximately 40 to 200 hr before the planned time of counting. (Potassium iodide is given orally just before iodoquine administration to block thyroid uptake of free ^{131}I ion.) Five to 24 hr before counting, 10 μc of ^{22}NaCl are administered intravenously. This isotope is distributed quite rapidly in the "water space." At the time of counting the iodoquine will be distributed in two general ways: a certain portion will be bound to pigmented tissues with the remainder (and major part) distributed throughout the body in a relatively nonspecific manner. Since only the melanin-bound iodoquine is informative, the simultaneous use of the ^{22}Na gives us a means of correcting for the counts due to the nonlocalized iodoquine.

Counting is then performed with a NaI(Tl)-crystal scintillation detector, the output of which is fed into two analyzer-scalers. These are adjusted to separately count the 0.364-Mev gamma of ^{131}I and the 0.51-Mev annihilation photon of ^{22}Na. The detector is suitably calibrated, and the observed iodine and sodium counts are corrected for the "cross-counting" effect to give the true iodine and sodium counts. The detector is then placed over several regions where, on clinical grounds, tumor is unlikely to be present—the mid-thigh, for example, if the primary had been on an upper extremity. The ratio of I/Na counts is averaged over several such uninvolved regions, and this value is used to correct the iodine counts over regions that are suspect. We have used a large detector (2 × 2-in. crystal) with various types of shielding for regional counting, and a small (¾ × ¾-in. crystal) probe for counting around selected areas such as the eye.

RESULTS

The results with this technique are illustrated by the following cases.

Case 1. A 65-year-old retired railway conductor with a history of having had a malignant melanoma excised from his right posterior shoulder 18 months previously presented with blurring of vision in the right eye, right-sided exophthalmos and two subcutaneous metastases on the face and neck (a third had been excised earlier and determined to be metastatic melanoma). He felt well otherwise. No further information was available to us at the time of the radioiodoquine study.

129 μc of ^{131}I-iodoquine were administered intravenously, and 96 hr later, 10 μc of ^{22}Na. Six hours later he was counted regionally with the large detector and later with the small probe, about the eyes. Using the small probe held in contact with the skin at the lateral canthus of each eye, the corrected ^{131}I counts (over a 10-sec interval) were 802 on the right side and 565 on the left. The ratios of the iodine to sodium counts were 9.78 and 4.32, respectively. Counts taken directly over the pupils were

* Obtained from New England Nuclear Corp. as an Investigational New Drug (IND 3703) in sterile and pyrogen-free form with a specific activity of 1 mc/mg.

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644 on the right and 611 on the left with I/Na ratios of 7.79 and 5.80. These data were interpreted as indicating the presence of an intra-orbital and probably retro-ocular melanoma. Regional counts over the thorax were interpreted as showing tumor in the right axilla and the right upper chest. From the marked liver uptake in this patient (compared with other patients) it was considered likely that he had liver metastases.

Physical examination revealed right axillary adenopathy. There was no hepatomegaly. Chest films were later reported as showing right mediastinal widening, a right paratracheal mass and a right-sided pleural effusion. Chemical studies were also performed, and a Thormahlen test for urinary melanogens (indole type) gave 42 μg indole/ml, the range of normal in our laboratory being 0–12 μg/ml. An experimental test for melanogens, the DPPH method (*3*), gave 365, the range of normal being 25–125. These results give further support to the iodoquine evidence of widespread dissemination of disease despite the lack of melanuria.

The patient then received a brief repeat course of hydroxyurea therapy but died about 1 month later. Autopsy revealed a right retro-ocular metastasis and widespread metastases in liver, kidneys, heart, lungs, pancreas and mediastinal nodes. Death resulted from pericardial effusion and tamponade.

Case 2. A 76-year-old retired oil-field worker had noted a progressive loss of vision in the left eye. At the time of his first ophthalmological examination he was noted to have advanced cataracts which interfered with the intra-ocular examination, and his refractive errors were corrected. He continued to have a progressive left visual loss and upon re-examination an intra-ocular mass was perceptible. The radioiodoquine examination was carried out with a 33-μc dose, and counts over the eyes at 16 hr were: 1,156 ± 47 on the right, 1,360 ± 33 on the left. At 49 hr the two isotope counts were taken and found to be

	Right	*Left*
^{131}I	1,119	1,294
$^{131}I/^{22}Na$	1.76	2.29

It was concluded that an iodoquine binding tumor, presumably a melanoma, was present in the left eye.

A clinical diagnosis of melanoma was made independently of these findings, and the eye was removed about 3 weeks later. It was found to contain an irregularly pigmented melanoma which at this time contained 3.4 dpm/mg (wet wt.) of radioactivity. The more deeply pigmented ciliary body contained 8.92 dpm/mg, and the other ocular tissues: vitreous —0.33, extra-ocular muscle—1.77 and optic nerve —1.52 dpm/mg. These measurements were all taken after several days of formalin fixation.

COMMENTS

This present technique has two limitations: first there is an elevated liver uptake (shown by chloroquine itself) so that liver metastases are difficult to detect, and later metabolic deiodination and biliary excretion of label raise the abdominal radioactivity for several days. It may be possible to overcome this by counting after an extended period or by using compounds other than iodoquine (*4,5*). The other limitation is both theoretical and obvious: a sufficiently small focus of tumor cells will necessarily be missed, as will tumors with insufficient pigment, and a patient cannot be told that he is absolutely free of tumor after a negative examination. Tiny (3–4 mm) melanomas in the anterior chambers of two patients were not detectable with the small unshielded probe. This is probably due to the limitations of the detector and the lack of appropriate collimating devices and ancillary equipment. In addition to these faults, our present regional counting system gives an inadequate spatial resolution. The improvement of this difficulty, however, is a straightforward physical problem. On the other hand, the radioiodoquine method adds indispensable information that cannot be gathered in any other way. Tumors that cannot be palpated or seen or visualized on x-ray have been detected with this technique.

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