Iodine-based liquid radiographic contrast agents were placed in normal and tumor-bearing (Greene strain) rabbit eyes to evaluate their ability to block iodine-125 radiation. This experiment required the procedures of tumor implantation, vitrectomy, air-fluid exchange, and 125I plaque and thermoluminescent dosimetry (TLD) chip implantation. The authors quantified the amount of radiation attenuation provided by intraocularly placed contrast agents with in vivo dosimetry. After intraocular insertion of a blocking agent or sham blocker (saline) insertion, episcleral 125I plaques were placed across the eye from episcleral TLD dosimeters. This showed that radiation attenuation occurred after blocker insertion compared with the saline controls. Then computed tomographic imaging techniques were used to describe the relatively rapid transit time of the aqueous-based iohexol compared with the slow transit time of the oil-like iophendylate. Lastly, seven nontumor-bearing eyes were primarily examined for blocking agent-related ocular toxicity. Although it was noted that iophendylate induced intraocular inflammation and retinal degeneration, all iohexol-treated eyes were similar to the control eyes at 7 and 31 days of follow-up. Although our study suggests that intraocular radiopaque materials can be used to shield normal ocular structures during 125I plaque irradiation, a mechanism to keep these materials from exiting the eye must be devised before clinical application. Invest Ophthalmol Vis Sci 31:1724-1730, 1990

Although most choroidal melanomas are treated with either observation, enucleation, or radiotherapy, there are many currently available options for treatment of intraocular tumors.1-15 While many patients with medium sized and some large melanomas are treated with radiotherapy, eyes are enucleated when the tumor is too large or has made the eye unsalvageable.9-15 Radiotherapy has been successful in stopping tumor growth, but reported complications include lash loss, dry eye, keratopathy, rubeosis, cataract, vitreous hemorrhage, radiation retinopathy, and optic neuropathy.9-18 These complications are closely related to the location of the tumor, its size, and therefore the amount of radiation given to adjacent normal ocular structures.

From the *Departments of Ophthalmology and §Radiology, North Shore University Hospital, Cornell University Medical College, Manhasset; the †Departments of Ophthalmology and Radiology, Cornell University Medical College, New York; and the ‡Medical Department, Brookhaven National Laboratory, Upton, New York.


The authors have no proprietary interest in the iodine-based radiographic contrast agents (blocking materials) discussed in this manuscript.

Reprint requests: Paul T. Finger, MD, Chief, Division of Ocular Tumor and Orbital Disease, Department of Ophthalmology, North Shore University Hospital, Cornell University Medical College, 300 Community Drive, Manhasset, NY 11030.

In 125I plaque therapy, radioactive seeds are fixed into a gold, bowl-shaped plaque which attenuates the radiation in all but one direction.10,11,19 Then this unidirectional source is sewn to the sclera over the base of an intraocular tumor. Once the plaque is in position, radiation passes through the sclera, into the intraocular tumor, vitreous, and finally through normal ocular structures before exiting the eye. If a radiation-blocking substance could be substituted in place of the vitreous, normal ocular structures could be protected during radiation therapy. Since metal objects are difficult to place and fix in position within the eye, we investigated vitreous replacement with radiopaque optically clear liquids. The amount of radiation attenuation provided by these materials was measured by thermoluminescent dosimetry (TLD), and the persistence of these materials was evaluated by serial computed tomographic (CT) imaging and densitometry readings.20-23 Although seven eyes were dedicated to an evaluation of toxicity, histopathologic examinations were performed on all 24 eyes for evidence of contrast-related ocular toxicity.

Materials and Methods

Experimental Model

This investigation adhered to the ARVO Resolution on the Use of Animals in Research. Our study required the use of 24 Giant Flemish rabbit eyes. Twenty-three eyes underwent vitrectomy, 19 with in-
insertion of an iodinated contrast materials, and five served as controls. Four of the 23 vitrectomized rabbit eyes were tumor bearing, and 19 were nontumor bearing (Table 1).

All procedures requiring sedation were done under anesthesia consisting of xylazine hydrochloride (20 mg/kg) together with ketamine hydrochloride (20 mg/kg). Proparacaine hydrochloride 0.5%, tropicamide hydrochloride 1%, phenylephrine hydrochloride 2.5%, and cyclopentolate hydrochloride 1% were administered topically before intraocular surgery.

The eyes for light microscopic examination were immediately fixed in cold buffered 10% formaldehyde. After 24 hr the eyes were vertically sectioned, alcohol dehydrated, and embedded in paraffin. The slides were stained with hematoxylin and eosin and evaluated in a masked fashion. All eyes were examined by light microscopy (Table 1).

Intraocular Tumor Model

The Greene strain of experimental melanoma was placed onto the choroid of four rabbit eyes and allowed to grow. Placement involved dissecting a scleral shelf 8–10 mm posterior to the corneoscleral limbus. When the red choroid was visualized a large (3 mm³) plug of tumor was placed within the scleral pocket and pushed onto the exposed choroid. The scleral flap was tightly sutured closed, and the field was irrigated with normal saline to protect against extrascleral extension. Typically, within 2–4 wk an intraocular melanoma would appear beneath the scleral implantation site. Observations of growth were monitored by indirect ophthalmoscopy and contact lens examination. Tumor sizes were recorded before vitrectomy and/or treatment. Relatively large tumors were selected for their ability to be seen on CT scanning.

Vitrectomy and Air–Fluid Exchange

Rabbits were anesthetized and the globe proptosed with a curved hemostat. Sclerotomies were done 4–6 mm posterior to the corneoscleral limbus, and an infusion cannula was sutured in the inferonasal quadrant. The eyes were vitrectomized under microscopic control with an irrigating contact lens. Core, axial, and peripheral vitrectomies were done on all rabbit eyes while trying to avoid contact with lens, retina, and tumor tissue. Lensectomy was required on three rabbit eyes due to significant lenticular damage during vitrectomy (Table 1). Cortical vitreous was removed as possible. After vitrectomy, an air–fluid exchange was done. The air was exchanged for either

<table>
<thead>
<tr>
<th>Table 1. Procedure Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbit eye no.</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Toxicty Study</td>
</tr>
<tr>
<td>1.</td>
</tr>
<tr>
<td>2.</td>
</tr>
<tr>
<td>3.</td>
</tr>
<tr>
<td>4.</td>
</tr>
<tr>
<td>5.</td>
</tr>
<tr>
<td>6. C</td>
</tr>
<tr>
<td>7. C</td>
</tr>
<tr>
<td>8. C</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TLD Dosimetry</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.</td>
</tr>
<tr>
<td>10.</td>
</tr>
<tr>
<td>11.</td>
</tr>
<tr>
<td>12.</td>
</tr>
<tr>
<td>13.</td>
</tr>
<tr>
<td>14. C</td>
</tr>
<tr>
<td>15. C</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Computed Tomography</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.</td>
</tr>
<tr>
<td>17.</td>
</tr>
<tr>
<td>18.</td>
</tr>
<tr>
<td>19.</td>
</tr>
<tr>
<td>20.</td>
</tr>
<tr>
<td>21.</td>
</tr>
<tr>
<td>22.</td>
</tr>
<tr>
<td>23.</td>
</tr>
<tr>
<td>24.</td>
</tr>
</tbody>
</table>

+ = Procedure performed; – = procedure not performed; C = control rabbit.
Fig. 1. The plastic envelope housing two square TLD chips is sewn to the episclera at the 12 o'clock position so that its center approximated the equator.

Fig. 2. An I-125 scleral plaque is sewn to the episclera at the 6 o'clock position so that its center approximated the equator.
iopamidol, iohexol, or iophendylate. The scleroto-
mies were closed with 8-0 nylon sutures, the conjun-
tiva was closed over the sclerotomy sites, and gen-
tamcin sulfate (20 mg) was injected subconjuncti-
vially at the end of the procedure.

Radiation-Blocking Agents

We investigated iophendylate, iohexol, and iopa-
midol as potential intravitreal radiation-blocking
agents. They differ in chemical composition, osmo-
larity, and percent iodine concentration. Iohexol and
iopamidol are water-soluble, nonionic contrast mate-
rials, and iophendylate is oil-like and therefore much
less miscible.

TLD

Lithium fluoride crystals are the TLDs most com-
monly used for clinical radiation dosimetry.23 We
used Harshaw TLD-100 chips which were 2 X 2 mm
square and 1 mm in thickness. A plastic envelope was
fashioned to house two TLD chips and was sewn to
the episclera at the 12 o'clock position so that its
center approximated the equator (Fig. 1). Then an
I25I scleral plaque was sewn to the episclera at the 6
o'clock position so that its center approximated the
equator (Fig. 2).

Two rabbit eyes served as controls, one for each of
the two I25I plaques used in this part of the study.
These eyes underwent vitrectomy without insertion
of the blocking agent before TLD. Values obtained
from these procedures were used for comparison with
intravitreal blocking agent-bearing eyes. Then five
rabbit eyes underwent vitrectomy with blocking-
agent insertion (iohexol-300, iohexol-240, iopami-
dol-300, and two iophendylate) before application of
an I25I plaque and TLD dosimeters. Iohexol-300 and
iopamidol-300 dosimetry was started within 2 hr of
contrast insertion and was continued for 2 hr. Iop-
phendylate dosimetry was performed within 4 hr of
contrast insertion and was continued for 2 hr. Last-
ly, one iohexol-240 dosimetry was done 168 hr after
blocker insertion (Table 2).

CT Imaging and Densitometry

A Picker 1200 SX CT (Cleveland, OH) scanner was
used to study the globes of contrast-bearing rabbit
eyes. With the rabbits prone and anesthetized, con-
tiguous 2-mm sections with a 2-mm slice thickness were
obtained in a semicoronal plane. The scan matrix was
512 X 512, and the scan angle was 398°. The radi-
ographic technique was kVp 130, MAS 455. Tumor-
bearing rabbit eyes were scanned to define the loca-
tion of the intraocular radiation-blocking agents with
respect to the experimental choroidal melanomas
(Fig. 3).

In an effort to describe how well these agents per-
sisted within the eye over time, serial densitometry
readings were performed on five rabbit eyes at 0, 12,
24, and 36 hr and at 5-7 days after contrast insertion
(Figs. 4, 5).

Results

All of the intraocularly placed radiographic con-
trast agents examined in this study were shown to
block I25I radiation in the rabbit eye (Table 2). As
measured by TLD the amount of radiation attenua-
tion provided by the blocking agents was not equal.
CT STUDY OF TRANSIT TIME
IOHEXOL DENSITY

Fig. 5. Serial densitometry readings (Hounsfield units) demonstrate the relatively rapid exit of the aqueous based iohexol from the normal rabbit eye.

With plaque #1 it appeared that the presence of intracocular iophendylate reduced the amount of radiation that crossed the aphakic rabbit eye such that approximately 90% of the radiation was attenuated compared with the control rabbit. With plaque #2 on a phakic rabbit eye, the iophendylate was slightly less effective, blocking 87% of the $^{125}$I radiation. The aqueous-based agents iohexol-300 and iopamidol-300 appeared to be less effective radiation blockers compared with iophendylate. When measured within the first 4 hours of intravitreal insertion, they blocked an average of 70.5% of the $^{125}$I radiation. When measured 168 hours after iohexol-240 insertion, little radiation-blocking effect was evident. This loss of effectiveness was explained in the second phase of this study.

Five contrast-bearing eyes were examined in a timed experiment where serial CT scans with densitometry readings of the intraocular contrast were done at 0, 12, 24, and 36 hours and/or 5–7 days. As illustrated by the serial densitometry readings, it appeared that the oil-like iophendylate persisted for 7 days with little dilution (Fig. 4). In comparison, the aqueous-based iohexol-300 exhibited what appeared to be a relatively rapid dilution within the first 12–24 hours after insertion (Fig. 5).

All 24 eyes were examined by light microscopy. Seven underwent vitrectomy, air–fluid exchange, and blocker insertion alone. No other procedures were performed on these rabbits, and they were killed at 7 or 31 days. Examination of one eye that received iophendylate and was followed for 7 days before enucleation was significant for vitritis and loss of photoreceptors in the inferior retina (Fig. 6), with relative sparing of the superior retina. The intraocular inflammation was more evident in the 31-day specimen with vitritis, scleritis, and marked degeneration of all retinal cellular elements (Fig. 7). Histologic evaluation of the iohexol-bearing rabbit eyes after 1 and 4 weeks of follow-up was equivalent to the two control rabbits (Fig. 8).

Conclusion

The $^{125}$I seeds emit gamma rays (28 keV) which interact with normal vitreous by coherent scattering (10%), photoelectric absorption (40%), and Compton scattering (50%).\(^{20-22}\) Only in photoelectric absorption does the 28 keV gamma ray give up all its energy to a tightly bound electron in the K-shell, thereby being locally absorbed. In the presence of the iodine-based contrast agent which has replaced the vitreous in this experiment, the probability of photoelectric absorption increases proportionally to its percent iodine content. The amount of attenuation or protective effect should also be dependent on the thickness

Table 2. TLD Dosimetry

<table>
<thead>
<tr>
<th>Rabbit</th>
<th>Transocular distance (mm)</th>
<th>Agent</th>
<th>Two TLD readings (nC)</th>
<th>Average dose (cGy)‡</th>
<th>Percent blocked†</th>
<th>Time elapsed (hr)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-125 plaque #1 on 4 aphakic rabbits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>19</td>
<td>Iophendylate</td>
<td>16.7/14.4</td>
<td>0.56</td>
<td>90</td>
<td>&lt;1</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>Iopamidol-3C0</td>
<td>53.9/53.5</td>
<td>1.92</td>
<td>67</td>
<td>&lt;1</td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>Iohexol-240</td>
<td>152.0/154.9</td>
<td>5.48</td>
<td>4</td>
<td>168</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>None</td>
<td>167.7/174.1</td>
<td>5.86</td>
<td>0</td>
<td>&lt;1</td>
</tr>
<tr>
<td>I-125 plaque #2 on 3 phakic rabbits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>19</td>
<td>Iophendylate</td>
<td>72.8/60.8</td>
<td>2.14</td>
<td>87</td>
<td>4.0</td>
</tr>
<tr>
<td>6</td>
<td>19</td>
<td>Iohexol-300</td>
<td>138.8/132.3</td>
<td>4.34</td>
<td>74</td>
<td>1.5</td>
</tr>
<tr>
<td>7</td>
<td>19</td>
<td>None</td>
<td>464.2/585.4</td>
<td>16.81</td>
<td>0</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

* Time elapsed (hr) is the time difference between injection of iodinated contrast agent and application of the radioactive eye plaque.
† Percentage of radiation blocked compared to the control rabbit in that group.
‡ After 2 hr of I-125 plaque application.
of the contrast medium or the distance between the plaque and the structure to be protected, and how quickly the material naturally exits the eye.

Although we showed that iodinated radiographic contrast materials can be used to block $^{125}$I plaque irradiation in vivo, one insertion would not be adequate for clinical application. In plaque radiotherapy of choroidal melanoma, apical dose rates (dose to the apex of the tumor) of greater than 150 cGy/hr are not recommended. So even with thermoradiotherapy where prescription doses of 50 Gy are used, it would take a minimum of 33 hours and 20 minutes to deliver the total dose. From our data the oil-like iophendylate was the only agent which persisted within the eye for this long a period; however this agent also caused unacceptable intraocular toxicity after 7 and 31 days of follow-up. Our data also suggest that up to six additional insertions of the well-tolerated aqueous-based iohexol would be required to maintain adequate intraocular concentrations for radiation protection. Therefore further studies using aqueous suppression techniques (eg, acetazolamide), continuous infusion, or intraocular balloons to maintain therapeutic intraocular concentrations of iohexol-300 will be required. When normal ocular structures are exposed to higher concentrations of iohexol for 36 hours, a reevaluation for intraocular toxicity will be required before clinical application.

We noted that intraocular blocking agents significantly attenuated $^{125}$I radiation before it reached the normal ocular structures which comprise the eye wall opposite from an episcleral $^{125}$I plaque. Although intravitreal radiation blocking will decrease radiation of normal ocular structures, the potential benefits of this technique must also be weighed against the possibility of complications due to vitrectomy, and the risk of manipulation of a tumor-bearing eye.

Key words: iodine-125, intraocular tumors, radiation protection, iohexol, iopamidol, iophendylate

References


