Use of radioactive bleomycin to detect malignant intracranial tumors

Comparative study with technetium-99m in 104 cases

LYSIANE MAMO, M.D., JEAN-PAUL NOUEL, M.D., JACQUES ROBERT, M.D., NICITHA CHAI, M.D., AND RAYMOND HOUDART, M.D.

Département de Gamma-Encéphalographie, Service de Neurochirurgie, Hôpital Lariboisière, Paris; Service des Radio-Isotopes, Centre Henri-Becquerel, Rouen; and Service d’Explorations Fonctionelles par les Méthodes Physiques, Faculté de Médecine, Nancy, France

A new isotopic method for the detection of cerebral tumors using labeled bleomycin is described. In a series of 104 patients, bleomycin was found superior to technetium-99m for the diagnosis of intracranial metastatic lesions; in 50% of the cases, bleomycin revealed metastases undetected by the Tc-99m, particularly in the posterior fossa. This method also provides valuable data for the differentiation of gliomas from metastases.

KEY WORDS • bleomycin • technetium-99m • brain tumors • brain scan • radioisotopes

Since the original work of Moore, using diiodo-fluorescein labeled with I131, the isotopic methods of detection and etiological diagnosis of cerebral tumors have improved considerably. There have been three stages in the evolution of gamma-encephalographic techniques. First came “contact gammagraphy,” whereby serum albumin labeled with I131 was used to count each point. With such recordings made 1 and 24 hours after the injection, it was possible to confirm the positive diagnosis and distinguish malignant from benign tumors with a rate of success of about 70%. Next came the scintillation method with automatic sweep which produced a three-dimensional image of the lesion, and coincided with the introduction of short-life isotopes, thereby reducing considerably the irradiation of the patient; positron emitters, radioactive mercury (Hg197 and 203-labeled neohydrin) and more recently technetium-99m, indium-113m, and ferrous ascorbate labeled with Tc-99m, have been used. In the present stage, the gamma camera has been coupled to a computing system, which enables a rapid sequential study of the distribution of the radioisotope in the first seconds and minutes after injection, thus providing more evidence for...
an exact etiological diagnosis.\textsuperscript{1,7}

Whichever recording technique is used with pertechnetate-99m, the principal risk in the interpretation of brain scanning has been "noise" introduced by the venous sinuses and the pericerebral tissues may mask a small neoformation. This major difficulty in the interpretation of brain scanning has been overcome by using labeled bleomycin. This antimitotic antibiotic, discovered by Umegawa in 1962, is totally nontoxic at the doses used in man in this study.\textsuperscript{9,10,20} It has two important advantages: a high affinity for potentially malignant tumors and a rapid plasma clearance\textsuperscript{9,12,13,18,21,22} Thus, bleomycin labeled with a gamma emitter, having a half-life sufficiently long for scintillographic examination to be made after 24 hours, provides a considerably increased concentration of radioactivity in the tumor and a better gammagraphic recording, free from all parasitic activity.

This report concerns the application of the bleomycin technique to the detection of malignant cerebral tumors.

**Method**

In this study we used bleomycin labeled with cobalt-57 by a technique developed by Renault, \textit{et al.};\textsuperscript{22} 15 mg of bleomycin, with an activity of 1 to 1.5 mCi of Co-57, were injected intravenously. The energy of this pure gamma emitter (122 keV) was very suitable for scintillographic exploration. Admittedly, the long physical half-life (265 days) was a disadvantage, but this was largely compensated by its rapid elimination through the kidneys; 80\% of the radioactivity was found in the urine in the first 24 hours as labeled bleomycin. Calculation of radiation exposure showed, therefore, that total patient irradiation was weak, about 2 rads for an injected dose of 1 mCi of Co-57 (irradiation of the liver, 0.5 rads; kidneys, 0.5 rads; bladder, 1 rad). It was imperative to collect and stock the urine passed during the first 24 hours.

Recordings were made by either conventional scanning or gamma camera. The scanning with automatic sweep (Mecaserto,\textsuperscript{*} with 3-inch crystal, 37-hole collimator), provided only a qualitative appreciation of the results. Sweep speed was 40 cm/min for bleomycin exploration, 60 cm/min for Tc-99m exploration. Exploration with the gamma camera linked to a computer enabled quantitative results to be obtained, in particular the ratio of tumor to healthy brain. This examination consisted of a 10-min recording 24 hours after the injection (average number of counts, 10,000 for a dose of 1.5 mCi of Co-57).

The first step consisted of making repeated scintillographic recordings 1, 6, 24, and 48 hours, and, in 20 cases, 8 days after the injection of labeled bleomycin. The results indicated that the maximal concentration of radioactivity in the tumor was obtained after 24 hours; bleomycin disappeared from the tumor after 4 to 5 days. Consequently, gammagraphic exploration with this material was carried out only after 24 hours.

A Tc-99m gammagraphic exploration, performed 1 and 3 hours after injection, preceded that with bleomycin in every case. Comparison was also made with the results of the usual neuroradiological investigations. The comparison between Tc-99m and bleomycin exploration was carried out in 104 patients afflicted with various intracranial pathological disorders: metastases (57 cases), gliomas (30 cases), meningiomas (9 cases), ischemic disorders (4 cases), tuberculomas (2 cases), and abscesses (2 cases).

**Results**

The results are summarized in Table 1.

**Metastatic Tumors**

In the demonstration of metastatic brain tumors, scintillographic exploration with bleomycin was markedly superior to that with Tc-99m. There was greater fixation in the tumor; in 50 cases out of 57, the mean ratio of number of counts in the tumor to that in healthy tissue was far higher than for the Tc-99m exploration (Fig. 1). Bleomycin demonstrated one or more metastases unnoticed after Tc-99m exploration (33 of 57 cases); in 26 cases these were hemispherical metastases, and in 19, tumors of the posterior fossa (Figs. 2, 3, and 4).
Radioactive bleomycin to detect malignant brain tumors

**TABLE 1**

*Efficiency of bleomycin compared with Tc-99m*

<table>
<thead>
<tr>
<th>Type of Lesion</th>
<th>No. of Cases</th>
<th>Intensity of Hyperfixation with Bleomycin Compared to Tc-99m</th>
<th>Mean Ratio of Counts Tumor/Healthy Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>metastasis</td>
<td>57*</td>
<td>greater in 60 cases (87.7%)</td>
<td>1.88 3.8</td>
</tr>
<tr>
<td>astrocytoma</td>
<td>5</td>
<td>no fixation in 2 cases (stages 1 and 2)</td>
<td>1.7 1.7</td>
</tr>
<tr>
<td>glioblastoma</td>
<td>23</td>
<td>equal fixation in 3 cases</td>
<td>1.9 2.8</td>
</tr>
<tr>
<td>oligodendroglioma</td>
<td>2</td>
<td>fixation equally poor in both cases</td>
<td>1.5 1.6</td>
</tr>
<tr>
<td>meningioma</td>
<td>9</td>
<td>poor; no bleomycin fixation in 7 cases</td>
<td>3.8 1.4</td>
</tr>
<tr>
<td>ischemia</td>
<td>4</td>
<td>poor fixation by both</td>
<td>2.8 1.9</td>
</tr>
<tr>
<td>tuberculoma</td>
<td>2</td>
<td>no fixation by either</td>
<td></td>
</tr>
<tr>
<td>abscess</td>
<td>2</td>
<td>no fixation by either</td>
<td></td>
</tr>
</tbody>
</table>

* Bleomycin detected 33 cases of metastasis, a 58% greater success than with Tc-99m.

scintillographic diagnosis with bleomycin was confirmed during surgery in 50 patients and anatomically in seven who died before surgery could be carried out.

**Glioblastomas**

In the preliminary study of 17 cases, all of which were verified by surgery, the aspect of the scans differed from that obtained with metastases: the hyperfixation focus was more diffuse and heterogeneous and, in 11, less intense than with Tc-99m exploration (Fig. 5). In contrast, a very intense fixation was noted with bleomycin in six cases of polymorphic glioblastomas.

**Astrocytomas**

In our 11 cases, the use of bleomycin enabled us to estimate the evolving tendency of the tumor. In five cases at Stage 1 or 2 (according to the classification of Kernohan and Sayre11), the fixation was nonexistent or the same as that after Tc-99m. On the other hand, in six malignant astrocytomas at Stage 4, the fixation was far denser than that of Tc-99m. The latter type of astrocytoma has been grouped with the glioblastomas in Table 1.

**Oligodendrogliomas**

In the two cases examined, the bleomycin fixation, like that of the Tc-99m, was poor.

**Meningiomas**

In seven cases there was little or no fixation in the tumor (Fig. 6). A denser fixation was noticed in two cases of recurring meningiomatosis: one patient had three operations in 10 years; the other, two operations in 4 years during the evolution of the tumor.

**Miscellaneous Lesions**

In ischemia, the fixation was always better with the Tc-99m. Bleomycin exploration was of no value in the demonstration of tuberculomas or abscesses.

**Discussion**

Two important facts contribute to the superiority of bleomycin in the detection of tumor metastases to the brain. First, the fixation intensity in the tumor is greater due to the biological characteristics of bleomycin. Its physiological behavior makes it a very suitable carrier of radioactivity for...
Mamo, Nouel, Robert, Chai and Houdart

FIG. 1. Metastases from a thyroid epithelioma. **Upper Left and Right:** Scans carried out 3 hours after injection of Tc-99m show a very weak focus in the left frontopolar, paramedial region. **Lower Left and Right:** Scans carried out 24 hours after bleomycin labeled with Co-57 show a more intense frontal focus and also reveal a second small, left rolandic metastasis (arrow).

detection of malignant expansive intracranial lesions. Its plasma clearance is very rapid; after 24 hours, the plasma activity falls to 2% to 3% of the initial value, resulting in a very weak level of cerebral activity, scarcely greater than the "baseline noise" of the detecting instruments. This substance is thus particularly advantageous in the detection of malignant tumors of the posterior fossa or the base of the skull. Second, the great affinity of bleomycin for tumors showing high mitotic activity explains why metastases undetected with the conventional Tc-99m examination could be demonstrated with this method. This factor is obviously important because it is essential to take account of the solitary or multiple nature of these metastatic tumors when deciding to operate.

The two methods used are, in fact, complementary. Technetium-99m is clearly the best radioactive tracer for the diagnosis of meningiomas, bleomycin fixation being weak or absent in this type of tumor. It is also quite definitely superior for glioblastomas. The usefulness of labeled bleomycin with these tumors perhaps lies in the possibility of defining more surely the malignant potential of the tumor, and especially of differentiating this type of...
Radioactive bleomycin to detect malignant brain tumors

Fig. 2. Metastases to the posterior fossa from a cancer of the bladder. **Left:** Scan after Tc-99m shows a weak focus of hyperactivity (arrow) in the left subtemporal region. **Right:** Scan after bleomycin shows a much more intense focus; in addition, another large metastasis is distinctly visible in the middle of the posterior fossa.

It therefore seems important to find short-lived gamma emitters, which could label bleomycin, thus facilitating and extending its usefulness in diagnosis.

**References**


Fig. 3. Metastasis from bronchial carcinoma. **Left:** Scan after Tc-99m shows no focus. **Right:** Scan after bleomycin shows two small foci of hyperfixation, one parasagittal rolandic, the other posterior temporal.
Fig. 4. Metastases from carcinoma of the breast. **Left:** Scan after Tc-99m shows a focus of hyperfixation in the left frontorolandic region; its appearance is not characteristic of a metastasis. **Right:** Scan after bleomycin shows the focus is clearly metastatic and also reveals a metastasis of the posterior fossa unnoticed during the Tc-99m exploration.

15. Moore GE: *Diagnosis and Localization of Brain Tumors: A Clinical and Experi-

Fig. 5. Frontocallosoal glioblastoma (anterior views). **Left:** Scan after Tc-99m shows a heterogeneous frontomedial focus. **Right:** Scan after bleomycin shows a much less intense focus.
Radioactive bleomycin to detect malignant brain tumors

Fig. 6. Falco-tentorial meningioma. Left: Scan after Tc-99m shows a clear focus in the tumor. Right: Scan after bleomycin shows no fixation in the tumor.

mental Study Employing Fluorescent and Radioactive Tracer Methods. Springfield, Ill, Charles C Thomas, 1953


This research was carried out under the auspices of the G.R.A.M.I. (Groupe de Recherches pour l'Application Medicale des Isotopes).

Address reprint requests to: Mme. L. Mamo, Département de Gamma-Encéphalographie, Service du Professeur Houdart, Hôpital Lariboisière, 2 rue Ambroise-Paré, Paris Xème, France.