

Technetium-99m Glucoheptonate in Brain-Tumor Detection: An Important Advance In Radiotracer Techniques

Jean Lévillé, César Pison, Yousri Karakand, Raymond Lemieux, and Bertrand J. Vallières

Hôtel-Dieu Hospital, University of Montreal, Montreal, Canada

We have compared [Tc-99m] sodium pertechnetate with Tc-99m glucoheptonate in 52 patients studied for various brain lesions. Flow studies as well as delayed scans were performed in all. Especially in primary and metastatic lesions of the posterior fossa, the diagnostic yield was improved by the delayed glucoheptonate (GH) scans. In contrast, no advantage of GH over pertechnetate could be detected in the study of infarcts or other ischemic lesions. Various hypotheses are discussed to explain the observed differences in behavior between the two tracers.

J Nucl Med 18: 957-961, 1977

This study compares [Tc-99m] sodium pertechnetate (Tc-O_4^-) with Tc-99m glucoheptonate (TcGH) in the diagnosis of brain lesions, especially metastases and tumors of the posterior fossa. The very different molecular behavior of these two tracers emphasizes metabolic concepts in brain scanning.

MATERIALS AND METHODS

Instrumentation. The study was conducted with two scintillation cameras: one with no data processor* and one with a dedicated data processor†. The latter was used to record the flow studies and to perform graphical and arithmetical analyses of regions of interest, whereas the former was used mainly to study the later behavior of the radionuclides.

Both instruments were checked daily for uniformity using a 1200-ml liquid flood phantom containing about 3 mCi of Tc-99m. This activity produced an average of 19,000 cps on System 70 and 5,000 cps on the Pho-gamma, which approximates the rate observed in patients. The photomultiplier tubes were tuned regularly in order to obtain the best response of the Pho-gamma and to prevent clinically deceptive artifacts from appearing on the flood-corrected frames of the System 70. In order to establish an in-depth resolution index, we imaged a bar phantom

at different source-to-collimator distances and recorded the loss of resolution. A minification factor was also calculated, using eight Co-57 "point" sources arranged in a circle 20 cm in diameter. Finally, background frames were recorded daily with and without the cot to warn us of any contamination of the cot or the detector.

Radionuclides. Fifty-two patients were evaluated with paired TcO_4^- and Tc-GH studies following the administration of 15-20 mCi of labeled agent. The timing schedule for the detection usually included an immediate study (less than 10 min) and delayed studies at 1, 2, 4, and as long as 9 hr after the i.v. injection. Sodium perchlorate (400 mg) was given 30 min before each administration.

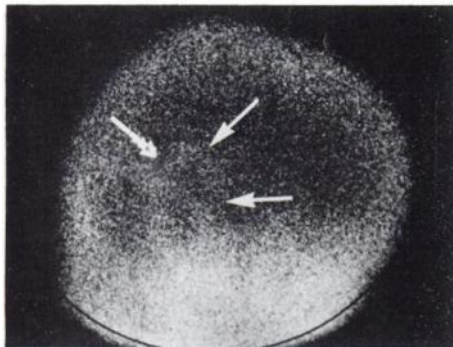
An interval of at least 48 hr was usually allowed between the two studies. The dynamic aspects of the cerebral blood flow were evaluated in anterior views by selecting equivalent regions of interest in each hemisphere and displaying their respective histograms.

Static brain studies were performed with the Pho-gamma or the System 70. Each Pho-gamma pro-

For reprints contact: Jean Lévillé, Nuclear Medicine, Hôtel-Dieu Hospital, 3840 St.-Urbain St., Montreal, Qué., Canada H2W 1T8.

TABLE 1. CASES STUDIED WITH GLUCOHEPTONATE AND PERTECHNETATE

Normal	12
Ischemia or infarct	10
Rejected	11
Proved brain tumors	7
Proved brain metastasis	12
Total	52

**FIG. 1.** "Ear artifact," seen more frequently with the glucoheptonate than with pertechnetate.

jection accumulated 200,000 counts; with the System 70 the maximum information density was set at 500. Routine static studies were obtained in the anterior, posterior, and right and left lateral projections, except when particular attention was necessary for a specific area of the brain.

RESULTS

A total of 52 patients were studied with both radioactive agents. Of these, 11 studies were excluded as incomplete. Most of these were out-patients from other hospitals for which we could not obtain adequate confirmation of the radioisotopic findings by neuro-radiologic, surgical or necropsy studies (Table 1).

Group 1 (Normal). Twelve patients had normal studies with TcO_4^- and $TcGH$, and these normal findings were confirmed either by the neuro-radiologic studies or by a minimum of six months of clinical followup. Most were investigated for headaches, psychiatric problems, or as a metastatic screening test. An ear artifact was frequently observed with $TcGH$ (Fig. 1). It has also been described with pertechnetate (1) but appears to be more frequent and important with $TcGH$.

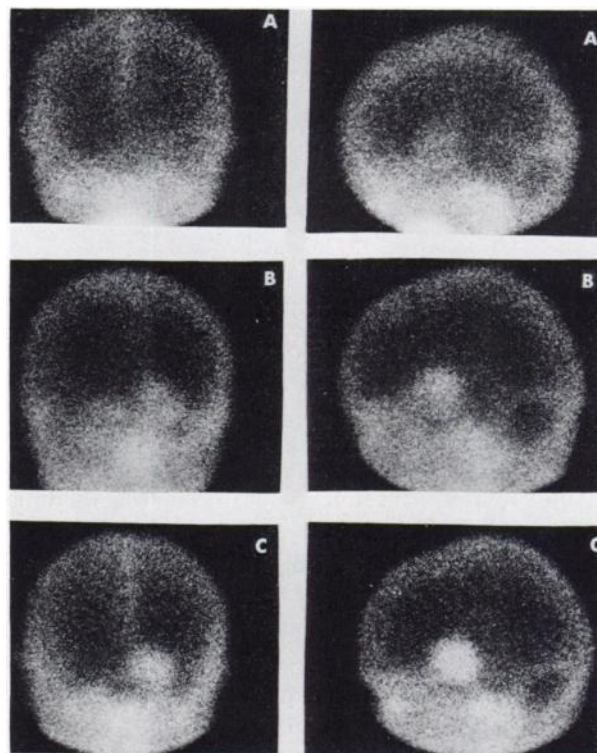
Group 2 (Primary tumors). Each of seven patients had surgery for a primary brain tumor (Table 2) and the diagnosis was confirmed by histologic find-

TABLE 2. CASES WITH BRAIN TUMORS

	Sex	Age	Pertechnetate*	Glucoheptonate*
Glioblastoma multiforme	M	53	±	+
Sarcoma	M	54	—	++++
Neurinoma	F	51	—	++++
Glioblastoma multiforme	F	70	+	++++
Sarcoma	F	63	ND	++++
Subdural hematoma	M	51	++	++
Meningioma	F	72	+	++++

* ± = low evidence to ++++ high evidence.
ND = Not done.

ings. The glucoheptonate showed better and progressive concentration in these tumors, and all the 4-, 6-, or 9-hr scans provided higher concentrations than earlier scans (Figs. 2 and 3). Technetium-99m GH imaging, delayed as long as 9 hours after injection, increased the true positive yield and was essential to establish the diagnosis in many cases. Brain background activity appears to be more stable

**FIG. 2.** Left temporal meningioma. In the 4-hr pertechnetate images (A), the anterior view is equivocal but the left lateral shows the tumor weakly. With glucoheptonate, the 2-hr images (B) visualize the tumor well, and at 4 hr (C) the target-to-nontarget ratio is still better.

with TcGH than with TcO_4^- , due mainly to the rapid clearance of TcGH from the blood. Many neoplastic lesions—especially in the posterior fossa—were missed in the TcO_4^- studies, even in scans delayed 4 or 6 hr after injection, but were visualized with TcGH (Fig. 4).

Group 3 (Metastatic lesions). Twelve patients had positive TcGH brain scans due to metastases (Table 3). We require gradual and "active" concentration of TcGH over a period of 4 to 9 hr, together with a minimum of two lesions, in order to establish a probability of metastatic disease. This gradual concentration of the TcGH was evaluated (Table 2) by the qualitative aspect of the lesions on the different delayed scans, or by quantitative evidence of the gradual rise of the target-to-nontarget activity ratio (Fig. 5). The TcO_4^- missed the metastatic lesions in six of the patients (Fig. 4).

Group 4 (Infarcts and other ischemic lesions). Ten studies revealed abnormalities compatible with a cerebral infarct or an ischemic lesion of the brain (Table 4). The dynamic blood-flow studies and the results of the static studies established the diagnosis. The dynamic blood-flow results were evaluated by histograms obtained from regions of interest in each hemisphere and showed important asymmetries after cerebrovascular accidents.

The results with TcGH and TcO_4^- were quite similar in circulatory lesions. In these we did not observe the gradual, progressive concentration of the TcGH, as we did in the tumors (Fig. 6). No difference between TcO_4^- and TcGH was observed in the flow studies.

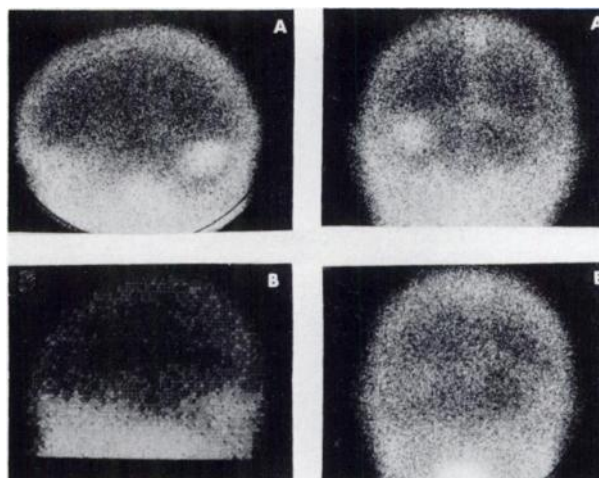


FIG. 4. Carcinoma of the breast: left lateral and posterior views of a metastasis in the posterior fossa. Glucoheptonate images (A)—even though rather early (3 hr)—established the diagnosis, whereas 5-hr pertechnetate images (B) failed to do so.

DISCUSSION

Since 1948 a large number of radiopharmaceuticals have been introduced for the purpose of brain scanning. The advent of TcO_4^- proved invaluable and soon gained universal approval for brain scanning (2).

Better results were obtained with delayed scans, which led to a number of hypotheses to explain its uptake mechanism. Many factors involved in the molecular dynamics of tracer concentration in the brain have retained our attention (3,4). Tracers can be concentrated in neoplastic tissue mainly as

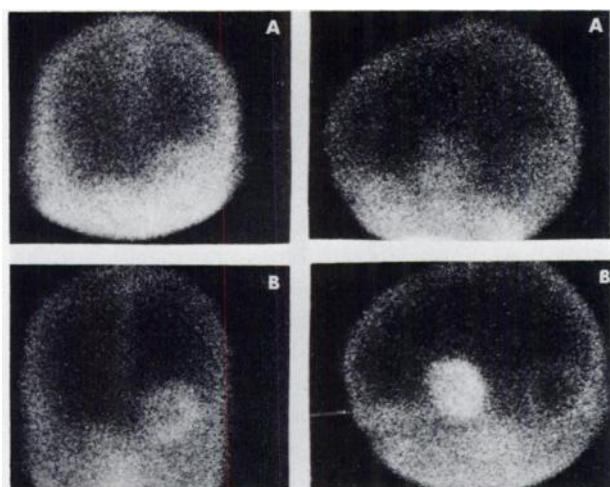


FIG. 3. Anterior and left lateral views of a left temporal meningioma. Four-hour pertechnetate images (A) show the tumor rather weakly; the situation becomes much clearer with the 5-hr glucoheptonate images (B).

TABLE 3. CASES WITH METASTASES

	Sex	Age	Pertechnetate*	Glucoheptonate*
Lung adenocarcinoma	M	59	+	+++
Lung cancer (unspecified)	M	67	±	+++
Adenocarcinoma (unknown origin)	M	71	++	++
Epidemoid epithelioma (lung)	M	54	+	+++
Oat cell carcinoma	M	54	±	++++
Breast carcinoma	F	39	+	++++
Adenocarcinoma of large intestine	F	60	+	+++
Malignant melanoma	F	66	±	++++
Lung cancer (unspecified)	F	61	±	++++
Lung cancer (unspecified)	M	51	+	++++
Lung cancer (unspecified)	F	72	±	++++
Lung cancer (unspecified)	M	65	±	++++

* ± = low evidence to ++++ high evidence.

substrates for growth, as substrates for energy, or by absorption as antigen-antibody complexes (3-5).

Studies with labeled glucose analogs indicate that tumors can extract large amounts of glucose (6-7). We were interested in the TcGH complex as a possible energy-producing substrate for the rapid metabolism of the brain tumors (9,10). This Tc-labeled saccharide is prepared from corn syrup (11) and shows no striking difference from the other saccharides in organ distribution, although their molecular weights vary (12).

The rapid blood clearance of the Tc-GH and the quite stable blood level (11-13) had led the first users to do their brain scans as early as 30 min—or at most 60 min—after the i.v. dose (11). Nevertheless, our study indicates a gradual, progressive uptake of the TcGH in the brain tumor together with a quite stable background, mainly due to the rapid blood clearance. In the majority of patients, the detection of two or three additional lesions was possible only with scans delayed up to 6 or 9 hr after the dose. In metastatic brain disease, the delayed studies generally permit the diagnosis to rise from mere suspicion to high probability.

The dynamic and static abnormalities in the stud-

TABLE 4. CASES WITH INFARCT OR ISCHEMIA

Sex	Age	Per technetate*	Glucoheptonate*
M	38	±	+++
M	68	++	++
F	52	+++	+
M	78	++	++
F	47	++	++
F	55	++	++
F	71	+	+
F	33	+++	+
F	66	+++	++
F	86	++	-

* ± = low evidence to ++++ high evidence.

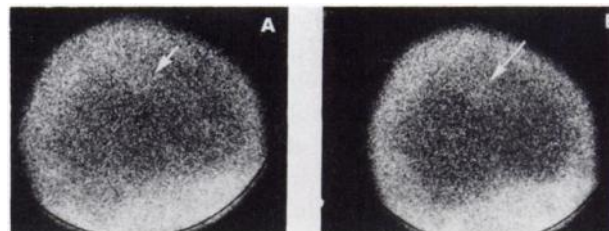


FIG. 6. Right parietal infarction. No differences are observed between the 3-hr per technetate (A) and the 5-hr glucoheptonate (B) images.

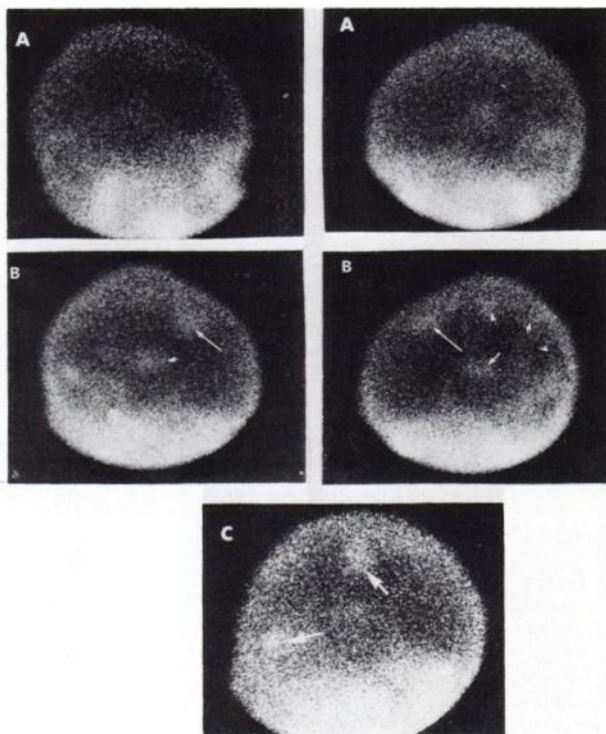


FIG. 5. Multiple metastases from carcinoma of the breast, right and left lateral projections. (A) Five-hour per technetate images indicate only the left parietal growth. (B) Four-hour glucoheptonate scintigrams clearly show five or six lesions. (C) Only the 9-hr glucoheptonate image (right, lateral) revealed "oat-cell" lesions in right parietal and occipital regions.

ies of cerebrovascular accidents were similar for the TcGH and TcO₄⁻, and we did not observe any progressive uptake of TcGH in infarcted cerebral tissue. Our study demonstrates that the concentration of the TcGH in the ear is more important than with TcO₄⁻ (7), and special attention must be focused on this artifact to avoid false-positive interpretations of GH scans. Nevertheless, our results clearly establish the superiority of TcGH over TcO₄⁻ for the visualization and identification of brain tumors, especially in metastatic disease.

The different results obtained with the TcGH and TcO₄⁻ contribute to reduce the importance of the theory of blood-brain barrier breakdown as a mechanism of radionuclide uptake in brain tumors. Our opinion is that GH contributes significantly to the detection of brain tumors because: (a) the GH molecular dynamics are different from those of TcO₄⁻ in neoplastic brain tissue but seem similar in infarcted brain tissue; and (b) there is a gradual uptake of the GH over a period of many hours in brain tumors in spite of the very rapid blood clearance.

Various authors have recognized the principal factors involved in the molecular radiopharmacokinetics of tumors are: (a) vascularity, (b) the interstitial fluid, (c) capillary permeability, and (d) the intracellular uptake (3).

The vascularity and the capillary permeability are surely among the earliest and most critical factors involved in radionuclide concentration in brain tumors, but the gradual uptake of TcGH over periods of hours must imply other mechanisms.

As a glucose analog, the TcGH is probably used as a substrate for energy by the tumor tissue. In view of the rapid blood clearance to a very low level, we must look for one or more intermediate steps between the vascular and the intracellular compartments. Biochemical and electron-microscope studies have shown that in almost all brain tumors there is much more interstitial fluid than in normal brain (14,15). The results with gluconate obtained by Boyd suggest the rapid filling of the extracellular fluid compartment and a subsequent release from it (13).

The important extracellular fluid compartment in a brain tumor could be responsible for the initial faint appearance of an abnormal zone that would represent an intermediate step between the optimal time of tumor visualization in our study and the rapid blood clearance of the TcGH.

The results obtained in animals (13) and humans (12) showed rapid diffusion into the extracellular fluid of the whole body, with subsequent release from the extracellular compartment. This could provide another intermediate step to explain the gradual uptake of the GH in the brain tumors.

The low blood level of the GH observed after an hour excludes any passive uptake mechanism, so the gradual accumulation in the brain tumors, demonstrated in our study, probably involves an active transport mechanism. As a glucose analog, the TcGH must be used as a substrate for energy by the tumor tissue.

ACKNOWLEDGMENTS

The authors wish to express their appreciation to the personnel of Nuclear Medical Service and Neurological Service, Hôtel-Dieu Hospital.

FOOTNOTES

* Searle HP Pho-gamma

† Baird Atomic System 70, Bedford, Mass.

REFERENCES

1. PATTON DD, BRASFIELD DL: "Ear" artifact in brain scans. *J Nucl Med* 17: 305-306, 1976
2. DI CHIRO G, ASHBURN WL, GROVE AS: Which radioisotopes for brain scanning? *Neurology* 18: 225-236, 1968
3. TATOR CH: Radiopharmaceuticals for tumor localization with special emphasis on brain tumors. In *Radiopharmaceuticals*, Subramanian G, Rhodes BA, Cooper JF, Sodd VJ, eds. New York, Society of Nuclear Medicine, 1975, pp 474-481
4. TATOR CH, MORLEY TP, OLSZEWSKI J: A study of the factors responsible for the accumulation of radioactive iodinated human serum albumin (RIHSA) by intracranial tumors and other lesions. *J Neurosurg* 22: 60-76, 1965
5. OLDENDORF WH: *Molecular criteria for blood-brain barrier penetration. Noninvasive brain imaging* 2: 17-23, 1975
6. GULLINO PM, GRANTHAM FH, COURTNEY AH: Glucose consumption by transplanted tumors in vivo. *Cancer Res* 27: 1031-1040, 1967
7. GULLINO PM, GRANTHAM FH, COURTNEY AH, et al: Relationship between oxygen and glucose consumption by transplanted tumors in vivo. *Cancer Res* 27: 1041-1052, 1967
8. TATOR CH, MORLEY TP, PAUL W: The pursuit of selectivity and refinement in the radioisotopic diagnosis of intracranial tumors. *Am NY Acad Sci* 159: 533-551, 1969
9. WAXMAN AD, TANACESCU D, SIEMSEN JK, et al: Technetium-99m glucoheptonate as a brain-scanning agent: Critical comparison with pertechnetate. *J Nucl Med* 17: 345-348, 1976
10. MAMO L, PANNECIERE C, PEREZ R: Intérêt du gluconate de calcium marqué au ^{99m}Tc dans la détection des tumeurs intra-crâniennes. *La Nouvelle Presse Médicale* 11: 795-797, 1975
11. *Product Monograph NRP 180*, Boston, New England Nuclear, Nov 1973
12. ARNOLD RW, SUBRAMANIAN G, MCAFEE JC, et al: Comparison of ^{99m}Tc complexes for renal imaging. *J Nucl Med* 16: 357-367, 1975
13. BOYD RE, ROBSON J, HUNT FC, et al: ^{99m}Tc gluconate complexes for renal scintigraphy. *Br J Radiol* 46: 604-612, 1973
14. ALEU FP, EDELMAN FL, KATZMAN R, et al: Ultrastructural and biochemical analysis in cerebral edema associated with experimental mouse gliomas. *J Neuropathol Exp Neurol* 23: 253-263, 1964
15. RAIMONDI AJ, MULLAN S, EVANS JP: Human brain tumors: An electron-microscopic study. *J Neurosurg* 19: 731-753, 1962