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IMPROVED BRAIN SCAN SPECIFICITY UTILIZING ^{99m}Tc-PERTECHNETATE AND ^{99m}Tc(Sn)-DIPHOSPHONATE

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Each of 36 patients was studied with two separate brain scans performed sequentially after the injection of 20 mCi of ^{99m}Tc-pertechnetate or 20 mCi of ^{99m}Tc(Sn)-diphosphonate. The resulting scans were qualitatively compared, and lesion-to-nonlesion ratios of activity determined. Diagnoses were established by clinical criteria and were supported in the majority of cases by computerized axial tomography or roentgen angiography or both. Histologic confirmation was available in five cases of tumor and in the single cases of subdural hematoma and cerebral abscess. Of 22 cerebral infarctions, 15 were better demonstrated with ^{99m}Tc-(Sn)-diphosphonate than with ^{99m}Tc-pertechnetate. Of the seven remaining cases, three were visualized equally well with each agent, and three were better demonstrated with ^{99m}Tc-pertechnetate. One was not seen with either agent. Of the 12 tumors, 11 were visualized better with ^{99m}Tc-pertechnetate than with ^{99m}Tc(Sn)-diphosphonate while in one case the lesion was seen equally as well with both agents. In no case was a lesion definitely seen with one radiopharmaceutical and not with the other. These results indicate that this dual method is helpful in differentiating gliomas and metastases from cerebral infarctions.

Technetium-99m-pertechnetate is the most widely used radiopharmaceutical for brain scanning. It is a sensitive agent for the detection of intracranial pathology but is nonspecific. Several other individual radiopharmaceuticals have been advocated to increase the diagnostic specificity of brain scanning (*1,2*) but multiple agents have not been utilized as commonly as in imaging other organs (*3*). A prospective study utilizing both ^{99m}Tc-pertechnetate and ^{99m}Tc-diphosphonate was undertaken to evaluate the recent observation that some cerebral infarctions are better defined with ^{99m}Tc-polyphosphate than with ^{99m}Tc-pertechnetate and that the reverse pattern may occur in cerebral tumors (*4,5*).

MATERIALS AND METHODS

Patients were selected for the study because of either a strong clinical suspicion of cerebral infarction or an abnormal ^{99m}Tc-pertechnetate scan performed for reasons other than a suspected cerebrovascular accident. Each patient had separate studies performed with the two agents. In the 22 patients diagnosed as having cerebral infarctions, scans were performed within 48 hr of each other in 18 cases, 72 hr in two cases, and 96 hr in two cases (Table 1).

Five-view brain scans were performed from 1 to 4 hr after the intravenous injection of either 20 mCi of ^{99m}Tc-pertechnetate as eluted from the generator or 20 mCi of ^{99m}Tc(Sn)-diphosphonate labeled by stannous chloride reduction of pertechnetate (*6*). Before the ^{99m}Tc-pertechnetate studies were performed, 500 mg of perchlorate were given orally, usually 250 mg the night before and 250 mg early on the morning of the study. The two scans were performed on similar equipment for each patient. Thirty-four patients were examined with a scintillation camera, and 300,000 counts were obtained for each view utilizing either an HP Searle Radiographics instrument equipped with a parallel-hole collimator (LEAP) or an Ohio-Nuclear Series 800 camera equipped with a 4,000 parallel-hole medium-energy collimator. Two patients were imaged with an Ohio-Nuclear dual scanner ("87" series) with 35L collimators at an approximate information density of 800 counts/cm^2.

Diagnoses were established by surgery in five of 12 cases of cerebral tumors and in the single cases of subdural hematoma and cerebral abscess (Table 1). In all except one case (MB) of suspected tumor and in 17 of 22 cases of cerebral infarction, the clinical diagnoses were supported by computerized transaxial tomography or cerebral roentgen angiography or both. The clinical course of the five remain-

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TABLE 1. PATIENT POPULATION AND FINDINGS

Patient	Diagnosis	Supporting evidence				Scan results	Days after acute event	
		CT	Art.	Surg.	Autopsy		TcP*	TcD†
Infarcts								
MB, 76F	Lt. MCA infarction	X				TcD >> TcP	45	46
MJ, 54M	Rt. MCA infarction		X			TcD >> TcP	49	50
JM, 49M	Lt. MCA infarction		X			TcD >> TcP	18	21
SM, 25F	Lt. MCA infarction		X			TcD >> TcP	12	11
SP, 55F	Rt. MCA infarction		X			TcD >> TcP	6	7
RR, 20M	Rt. MCA infarction with hemorrhage	X	X			TcD >> TcP	8	7
JT, 76M	Rt. PCA infarction		X			TcD >> TcP	52	53
LA, 67M	Lt. MCA infarction	X	X			TcD >> TcP	5	7
MC, 72F	Rt. MCA infarction		Clinical course			TcD > TcP	2	3
HD, 51M	Lt. occipital lobe infarct		Clinical course			TcD > TcP	150	151
AH, 83M	Rt. putamen hemorrhage	X			X	TcD > TcP	12	11
BK, 45F	Lt. MCA infarction	X	X			TcD > TcP	11	12
GM, 75F	Rt. MCA infarcts		X			TcD > TcP	11	12
MM, 87F	Rt. MCA infarct		Clinical course			TcD > TcP	5	6
CS, 63M	Lt. MCA infarct		Clinical course			TcD > TcP	28	29
DH, 65F	Lt. MCA infarct		X			TcP = TcD	13	11
MM, 75F	Rt. MCA infarct		Clinical course			TcP = TcD	10	9
FL, 64F	Rt. MCA infarct		X			TcP = TcD	10	6
HH, 72M	Lt. frontal infarct and hemorrhage	X	X			TcP > TcD	3	5
JJ, 31M	Lt. MCA infarct		X			TcP > TcD	24	26
MP, 69M	Rt. MCA infarct	X				TcP > TcD	48	52
EY, 72F	Rt. PCA infarction	X	X			No abnormality	7	10
Tumors								
JC, 72M	Metastatc squamous cell carcinoma (lung)	X				TcP > TcD		
EH, 68F	Metastatc squamous cell carcinoma (lung)	X				TcP > TcD		
MB, 50F	Metastatic melanoma	X-ray evidence of mets to lung, lymph nodes, and bone				TcP > TcD		
FS, 63F	Reticulum cell sarcoma		X	X		TcP > TcD		
JM, 80M	Astrocytoma	X	X			TcP > TcD		
JC, 35F	Astrocytoma	X	X			TcP > TcD		
CM, 32F	Astrocytoma		X	X		TcP >> TcD		
OO, 64F	Astrocytoma	X	X	X		TcP >> TcD		
AB, 59M	Astrocytoma	X	X			TcP >> TcD		
HC, 63F	Glioblastoma multiforme	X	X	X		TcP >> TcD		
CN, 66M	Metastatic adenocarcinoma primary unknown)	X	X	X		TcP >> TcD		
ES, 52F	Metastatic breast carcinoma	Known metastatic breast carcinoma to bone				TcP = TcD		
Other lesions								
JD, 45M	Cerebral abscess	X	X	X		TcP = TcD		
YL, 70M	Subdural hematoma	X	X	X		TcP > TcD		

* ^{99m}Tc pertechnetate.
† ^{99m}Tc(Sn) diphosphonate.
MCA is middle cerebral artery, PCA is posterior cerebral artery, ACA is anterior cerebral artery, > is slightly greater than, and >> is markedly greater than.
CT, computerized axial tomography; Art., cerebral arteriography.

ing patients with cerebrovascular disease was deemed to be so characteristic that it was considered valid to include them in this study.

In the final analysis of all the scans, three of the authors independently assessed the target-to-nontarget ratios of activity by gross visual inspection of the images. In this semiquantitative evaluation, the cases were categorized as to whether the activity with ^{99m}Tc(Sn)-diphosphonate was equal to, greater than, or less than that seen with ^{99m}Tc-pertechnetate. If a target-to-nontarget difference was recognized, the studies were further subdivided as to whether the difference was "slight" or "marked". In cases where there was disagreement among the authors, the option was chosen that minimized the difference between the scans. Thus, if disagreement existed as to

TABLE 2. SUMMARY OF RESULTS

Target-to-nontarget activities	Diagnoses: Infarction (21 patients)*	Tumors (12 patients)	Abscess (1 patient)	Subdural hematoma (1 patient)
^{99m}Tc(Sn)-diphosphonate >> ^{99m}Tc-pertechnetate	8	0	0	0
^{99m}Tc(Sn)-diphosphonate > ^{99m}Tc-pertechnetate	7	0	0	0
^{99m}Tc(Sn)-diphosphonate = ^{99m}Tc-pertechnetate	3	1	1	0
^{99m}Tc-pertechnetate > ^{99m}Tc(Sn)-diphosphonate	3	6	0	1
^{99m}Tc-pertechnetate >> ^{99m}Tc(Sn)-diphosphonate	0	5	0	0

* One cerebral infarction was not visualized with either agent and is not included in this tabulation.

whether a pair of scans demonstrated a "marked" difference or a "slight" difference, this was recorded in the data as "slight" difference. This situation arose in three cases.

RESULTS

Results are summarized in Table 2. The target-to-nontarget ratio in cerebral infarction was markedly greater with ^{99m}Tc(Sn)-diphosphonate than with ^{99m}Tc-pertechnetate in eight cases (Fig. 1), slightly greater in seven cases, equal in three cases, and slightly less in three cases. Neither agent visualized an occipital lobe infarction in patient EY.

In contrast to cerebral infarction, the target-to-nontarget ratio was greater with ^{99m}Tc-pertechnetate than with ^{99m}Tc(Sn)-diphosphonate in 11 of 12 patients with suspected or proved tumors. This was markedly so in five cases (Fig. 2). In one case (ES) the activities were considered equal.

In the one case of chronic subdural hematoma, the ^{99m}Tc-pertechnetate scan showed slightly greater lesion-to-nonlesion activity than ^{99m}Tc(Sn)-diphosphonate. The lesion-to-nonlesion ratio of activities was judged equal in the one case of cerebral abscess. In none of the four types of lesion studies was any lesion definitely seen with one radiopharmaceutical and not with the other agent.

DISCUSSION

The bone-scanning agents ^{18}F as fluoride and ^{99m}Tc(Sn)-polyphosphate were the first reported to accumulate in cerebral infarctions (*5*). Wenzel and Heasty (*4*) confirmed these findings and reported two cases of cerebral infarction in which the lesions were seen with ^{99m}Tc(Sn)-polyphosphate better than with ^{99m}Tc-pertechnetate and two cerebral tumors in which the opposite relationship was true. Jones, et al (*3*), in a study evaluating multiple agents for brain scanning, observed that three out of three intracranial metastatic tumors were better demonstrated with ^{99m}Tc-pertechnetate than with ^{99m}Tc(Sn)-polyphosphate.

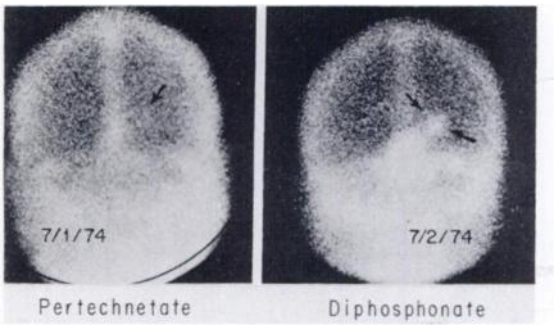

FIG. 1. Technetium-99m-diphosphonate brain scan demonstrates markedly increased activity in this patient's right occipital lobe infarction (arrows) as compared with ^{99m}Tc-pertechnetate study (both posterior views). This 76-year-old man (JT) developed left inferior quadrant anopsia 1½ months prior to these studies. Cerebral arteriogram performed June 30, 1974 (2 days before brain scan) showed occlusion of right posterior cerebral artery and extensive atherosclerotic changes in intracerebral vasculature.

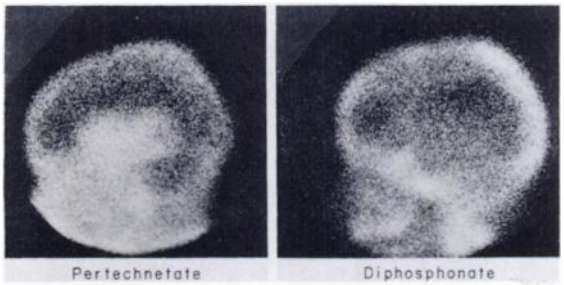

FIG. 2. Comparison of left lateral brain scans with two agents shows markedly better demonstration of this patient's Grade III astrocytoma with ^{99m}Tc-pertechnetate than with ^{99m}Tc(Sn)-diphosphonate. This 32-year-old woman (CM) presented 14 months after partial removal of Grade III astrocytoma. Cerebral angiogram demonstrated tumor vascularity involving deep left frontotemporal area with extension into left hypocampus and lateral basal ganglia.

An abnormal increase of radionuclide within an intracranial lesion as seen on a ^{99m}Tc-pertechnetate brain scan is mainly the result of two processes: (A) a disruption in the blood-brain barrier allowing substances usually excluded from normal brain tissue to diffuse into a lesion; and (B) an increase in vascularity (blood pool). Although an intracellular accumulation has been reported in some acoustic neuromas (*7*), ^{99m}Tc as pertechnetate is generally considered to accumulate within the extracellular

fluid space of tumors (*8*). The site of accumulation of ^{99m}Tc(Sn)-diphosphonate in cerebral lesions is not known.

Of the infarctions visualized in this series, 71% (15/21) were better delineated with ^{99m}Tc(Sn)-diphosphonate than with ^{99m}Tc-pertechnetate. This appeared to be unrelated to the size or site of the lesion or the time of scanning after injection. However, in the early postinfarction cases (within 10 days of the event), the data might suggest that the order of scanning may affect the results. In both cases (MM, FL) in which equal activity was noted in the lesions, ^{99m}Tc-diphosphonate was given first. In the cases performed during this early period in which ^{99m}Tc-pertechnetate was given initially, four of five showed comparatively increased accumulation of the ^{99m}Tc-diphosphonate in the lesion. However, Cases RR and HH are examples in which the first radiopharmaceutical given showed the greater accumulation of activity within the lesion. No firm conclusions can be drawn from such small numbers of cases but a more critical factor than the order of scans in this early postinfarction period may be the time between scans. The local anatomic and physiologic factors determining the extent of accumulation of the radiopharmaceutical may be rapidly changing during this period. Waiting 96 hr as in Case FL may negate the value of this dual scanning system and favor increased accumulation of the radiopharmaceutical given last.

This differential accumulation within cerebral infarction has not been reported with other chelates such as ^{99m}Tc-DTPA and ^{113m}In-DTPA as compared with ^{99m}Tc-pertechnetate. Therefore, it is unlikely that the striking accumulation observed with ^{99m}Tc-diphosphonate can be attributed to the faster clearance from the blood which occurs with chelates (*9–11*). That some lesion specificity for the accumulation of ^{99m}(Sn)-diphosphonate exists in infarcted tissue is suggested by the finding that ^{99m}Tc-(Sn)-pyrophosphate and ^{99m}Tc(Sn)-diphosphate accumulate in myocardial infarctions (*12,13*). After myocardial infarction, calcium and phosphate ions enter necrotic tissue and form minute crystalline deposits which by electronmicroscopy resemble hydroxyapatite, the mineral matrix of bone (*14*). As with bone visualization, the radiopharmaceutical is believed to chemisorb onto these mineral accumulations (*12*). An analogous process may occur in cerebral infarction but there is no autoradiographic or other experimental evidence to prove this.

Of 12 tumors, 11 showed greater ^{99m}Tc-pertechnetate lesion-to-nonlesion activity than did ^{99m}Tc(Sn)-diphosphonate. These included suspected and proved primary as well as metastatic tumors. All the primary tumors confirmed by biopsy were high-grade astrocytomas. The confirmed metastatic tumor was an adenocarcinoma of unknown primary origin. No meningiomas were included in this group of patients. Data to be published subsequently by this laboratory demonstrate that unlike gliomas and intracerebral metastatic lesions, some meningiomas are better demonstrated by ^{99m}Tc(Sn)-diphosphonate than by ^{99m}Tc-pertechnetate.

Obviously, when interpreting ^{99m}Tc(Sn)-diphosphonate cerebral scans, one must be wary of areas of increased activity not related to intracranial pathologic conditions. Fractures, contusions, Paget's disease, calvarial metastases, and operative bone flaps are all delineated by ^{99m}Tc(Sn)-diphosphonate. Radioactivity along the coronal suture can be pronounced as a normal variant. Correlation of abnormal brain scans with skull radiographs is essential.

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