Differential Accumulation of Tc-99m DTPA and Tc-99m Pyrophosphate within Cerebral and Cranial Lesions: Concise Communication

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We sought to determine the clinical utility of using a bone-scanning agent in addition to a brain-scanning agent for the imaging of cerebral and cranial lesions. Images were obtained in 51 patients with Tc-99m diethylene-triamine-pentacetic-acid (DTPA) followed by Tc-99m pyrophosphate (PPi) within 2–5 days. The scans were qualitatively analyzed and the lesion-to-background count density ratios were determined from the corresponding brain and skull images. Only four of 20 cerebral infarctions were better demonstrated with PPi, whereas they were better with DTPA in 14 patients. They were equally good in two patients. The average lesion-to-background count-density ratio for infarction was 1.555 ± 0.335 with DTPA and 1.428 ± 0.573 with PPi ($p > 0.05$). Primary brain tumors were better visualized with DTPA in four out of five cases ($p < 0.05$). Metastases to brain showed up better with DTPA in 15 of 16 patients ($p < 0.05$), whereas all ten metastases to skull were seen better with PPi ($p < 0.01$).

These results support previous reports regarding the radiopharmaceutical of choice for tumor imaging but not for infarction. This may be due to the differences in blood clearance for the various imaging agents.

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A variety of adjunctive radiopharmaceuticals, including Tc-99m-labeled bone-imaging agents, have been used to aid in the differential diagnosis of lesions detected in routine brain images. This differentiation is especially important when there is a question of whether the lesion is located in the skull, the meninges, or the brain itself in patients with metastatic disease. There are also many cases in which cerebral infarcts have an atypical scan appearance and cannot be differentiated from tumor without invasive study. Transmission computerized cranial tomography (TCT) has been utilized to distinguish ischemic cerebral infarction from cerebral hemorrhage or subdural hematoma. However, in some cases, during the liquefaction of cerebral infarcts and in the subacute transition stage of subdural hematoma, the lesions will approach the same density as the adjacent brain and may show little or no contrast even with enhancement.

There have been several reports of improved brain-scan specificity for cerebral infarction using [^{99m}Tc] sodium pertechnetate (TcO_4) and Tc-99m polyphosphate or diphosphonate bone-scanning agents (*1–3*). The majority of infarcts were better demonstrated with the bone-scanning agents, whereas most brain tumors were seen better with TcO_4. This differential accumulation within cerebral lesions has not been reported comparing a bone-scanning agent with DTPA, a chelated compound increasingly used for brain imaging.

The purpose of this study was to evaluate images of cerebral and cranial lesions, comparing DTPA with PPi, which has been the most widely used infarct-imaging agent.

MATERIALS AND METHODS

Fifty-one patients with DTPA brain-scan abnor-

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malities were re-imaged with PPi 2–5 days later. Both the brain- and skull-imaging studies were performed approximately 3 hr after i.v. injection of 20 mCi of DTPA or 15 mCi of PPi. Four routine head views (500 K counts each) were obtained with a gamma scintillation camera equipped with low-energy converging collimator. All scans were analyzed qualitatively by one of us (E.E.K.) using the usual visual criteria, and the target-to-background ratios for count density were determined using a densitometer.* Densitometry readings were taken from the corresponding brain and skull images using the central portion of each lesion. Count densities were obtained from an empirically determined calibration curve relating film optical density to count density. Statistical analysis was performed by Student's t-test with paired observations. Seventeen of the 20 cases of cerebral infarction were evaluated by TCT. Histological diagnoses were obtained for all of the primary brain tumors. Diagnoses of metastases to the brain or skull were supported by TCT, skull radiographs, and at least 6 mo of clinical follow-up.

RESULTS

Table 1 summarizes the analytic results. Only four of 20 cerebral infarctions were better demonstrated with PPi than with DTPA. Cerebral infarcts were better defined with DTPA in 14 patients; images of equal quality were obtained with the two agents in two cases. The average ratio of lesion-to-background count density for cerebral infarction was 1.555 ± 0.335 in brain images and 1.428 ± 0.573 in skull images ($p > 0.05$). All of the patients with cerebral infarction were scanned within 5–20 days of the onset of neurological symptoms or signs. Within this time range, there appeared to be no significant relationship between the time of onset and the imaging results. The results also appeared to be unrelated to the size or site of a lesion. TCT with contrast enhancement yielded normal findings in four of 17 patients with cerebral infarction, and the findings were equivocal in two others. Primary brain tumors were seen better with DTPA than with PPi in four out of five cases (all glioblastomas), and with equal visualization in one case. The average ratio of lesion-to-background count density for primary brain tumor was 2.416 ± 0.828 in brain images and 1.214 ± 0.2 in skull images ($p < 0.05$). Metastatic tumors to brain were better demonstrated with DTPA in 15 of 16 patients, whereas all ten metastatic tumors to skull were seen better with PPi. The average ratio of lesion-to-background count density for metastases to brain was 1.666 ± 0.596 in DTPA scans and 1.235 ± 0.264 in PPi scans ($p < 0.05$). Metastases to skull showed an average lesion-to-background count-density ratio of 1.321 ± 0.31 in DTPA scans and 2.611 ± 0.942 in PPi scans ($p < 0.01$).

DISCUSSION

Previous workers have sought to extend the use of bone-seeking agents (polyphosphonates or diphosphonates) to the study of cerebral infarction, comparing these findings with those obtained from pertechnetate. Since DTPA has been proven to be superior to TcO_4 for brain imaging (*4*), we chose it as the brain agent in this study. Similarly, we chose PPi as the bone agent because of its documented greater avidity for myocardial infarcts than various other bone-scanning agents (*5*). This choice of radiopharmaceuticals prevents direct comparison of our findings in cerebral infarct imaging with those of other investigators, but it is possible to speculate that the use of different agents accounts for the difference in the results obtained. While our results agreed with the others in regard to tumor imaging, our findings in cerebral infarction did not agree with these earlier reports.

Grames et al. (*1*), evaluating the lesion-to-background activity ratios in six patients with cerebral infarction, using TcO_4 and hydroxyethylidene diphosphonate (HEDP), obtained an average ratio of 2.6 with TcO_4 and 4.4 with HEDP. Fisher et al. (*2*) reported similar results

TABLE 1. DIFFERENTIAL ACCUMULATION OF Tc-99m DTPA AND Tc-99m PPi WITHIN VARIOUS CEREBRAL AND CRANIAL LESIONS

Comparison of DTPA and PPi uptake on images	Cerebral infarction (20)	Primary brain tumors (5)	Metastasis to brain (16)	Metastasis to skull (10)
DTPA ≫ PPi	5	1	6	0
DTPA > PPi	9	3	9	0
DTPA ≒ PPi	2	1	0	0
DTPA < PPi	2	0	1	1
DTPA ≪ PPi	2	0	0	9
Av. count density ratio of lesion to background				
Brain images	1.555 ± 0.335	2.416 ± 0.828	1.666 ± 0.596	1.321 ± 0.31
Skull images	1.428 ± 0.573	1.214 ± 0.2	1.235 ± 0.264	2.611 ± 0.942
Paired Student's t-test	$p > 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.01$

in 21 patients with cerebral infarction using TcO_4 and a diphosphonate (DP), with greater uptake of DP than TcO_4 in 15, equal uptake in three, and less uptake of DP than TcO_4 in one case. Wenzel et al. (*6*) also found a bone-scanning agent, polyphosphate (PP_x), superior to TcO_4 for infarct detection in the brain.

Entry of PP_x into the extracellular space of lesions has been documented autoradiographically (*7*). Aware of the studies of D'Agostino et al. (*8*) on mitochondrial mineralization in irreversible myocardial ischemic damage, Bonte et al. (*9*) investigated and introduced PPi as an imaging agent for acute myocardial infarction, a practice that is now established. They postulated that PPi localizes in a crystalline structure within the mitochondria of irreversibly damaged myocardial cells. Perhaps some combination of facilitated entry into the extracellular space (altered blood-brain barrier) and active intracellular localization accounts for the ability of these bone-scanning agents to localize in cerebral infarcts.

The difference in blood clearance rates of the radiopharmaceuticals appears to be responsible at least in part for the result in this study of the superiority of DTPA over PPi for cerebral infarct imaging. PPi shows greater protein binding—and hence slower renal excretion from the blood stream—than DP or HEDP, while DTPA has a faster renal clearance than TcO_4 (*4,10*). Utilization of both DTPA and PPi for imaging cerebral infarcts does not appear to be clinically useful, although previous studies, as well as ours, have not taken into account the exact stage of cerebral infarct development at the time of cerebral imaging.

FOOTNOTE

* Model 301, X-Rite Co.

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