Cerebral Blood Flow Imaging with Thallium-201 Diethyldithiocarbamate SPECT

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Thallium-201 diethyldithiocarbamate ([^{201}Tl]DDC) was studied in humans as an agent for cerebral blood flow imaging. Brain uptake proved to be complete 90 sec after injection with no appreciable washout or redistribution for hours. Intracarotid injection suggested an almost 100% extraction during the first passage. Whole-body distribution studies demonstrated a brain uptake of 4.3% of the dose compared with 0.9% for [^{201}Tl]chloride. No differences were found in the distribution of [^{201}Tl]DDC versus [^{201}Tl]chloride in other organs. After the injection of 3 mCi ^{201}Tl, good quality single photon emission computed tomographic (SPECT) images of the brain were obtained with both a rotating gamma camera and a multidetector system. In ischemic brain disease, perfusion defects were easily demonstrated. We conclude that [^{201}Tl]DDC is a suitable radiopharmaceutical for SPECT studies of cerebral blood flow.

J Nucl Med 28:178–183, 1987

Sodium diethyldithiocarbamate (NaDDC), a metabolite of disulfiram, binds mono, bi-, or trivalent metallic ions easily, and has clinically been used in nickel poisoning (*1*), Wilson's disease (*2,3*), and thallium intoxication (*4,5*). It is used as a reagent for the colorimetric determination of copper. It has been observed during NaDDC therapy of thallium intoxication that neurologic symptoms sometimes worsen, which was credited to the increased lipophilicity of the thallium-DDC chelate with subsequent passage of the intact blood brain barrier (*6*). Vyth et al. (*7*) demonstrated approximately a tenfold increase in thallium-201 [^{201}Tl]DDC brain uptake in comparison to [^{201}Tl]chloride in rats.

Recently we reported in a comparative study of [^{201}Tl]DDC and N-isopropyl-p-iodine-123-iodoamphetamine ([^{123}I]IMP) in rabbits (*8*). We found that [^{201}Tl]DDC had a more instant brain uptake, and reached equilibrium at an earlier time, while it was not retained by the lung. Now we report on the uptake and distribution of [^{201}Tl]DDC in human and the application of [^{201}Tl]DDC single photon emission computed tomography (SPECT) in the normal human brain and in acute ischemic disease. In acute ischemic brain disease defects could easily be demonstrated with [^{201}Tl]DDC SPECT without appreciable redistribution for hours. We provide evidence that [^{201}Tl]DDC is a real flow marker, which behaves like a "chemical microsphere."

Received Jan. 9, 1986; revision accepted June 19, 1986.

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MATERIALS AND METHODS

Thallium-201 DDC Preparation and Quality Control

Fifty milligrams of NA-DDC 3 H_2O was dissolved in 10 ml of sterile saline. The solution was sterilized by passage through a 0.2-μm membrane filter. Thallium-201 DDC was prepared by the addition of 1 ml [^{201}Tl]chloride, containing 4 mCi to 2 ml of the NaDDC solution. The mixture was injected after a short incubation period of 5 min. Labeling efficiency, which was >95%, and lipophilicity were tested on ITLC strips eluted with methylethylketone, as described previously (*8*).

Human Studies

All human studies were done after obtaining informed consent and approved by the Medical Ethical Committee in both hospitals. The studies performed in the New England Deaconess Hospital were approved by a physician sponsored IND of the FDA. All patients with a history of acute stroke were submitted to both [^{201}Tl]DDC SPECT and computed

tomography (CT) without contrast enhancement. Computed tomographic studies were performed within 24 hr of the [^{201}Tl]DDC studies. Direct comparison was made of areas showing diminished activity on the SPECT study with hypodense areas on the CT.

Thallium-201 DDC Whole-Body Scans

Anterior and posterior whole-body images were obtained in five normal human volunteers 1 hr after the injection of 3–4 mCi [^{201}Tl]DDC with a rotating gamma camera† mounted with a high resolution collimator. Regions of interest were marked around brain, heart, liver, kidneys, salivary glands, and thyroid. The percentage of uptake was assessed by calculating geometric counts and compared with geometric whole-body counts after correction for background. Data were compared with [^{201}Tl]chloride distribution in five subjects, who underwent a [^{201}Tl]chloride cardiac study.

Thallium-201 DDC Brain Uptake and [^{201}Tl]DDC SPECT

In four normal human volunteers and nine patients suffering from acute unilateral ischemic brain disease, brain uptake curves were obtained after the i.v. injection of [^{201}Tl]DDC for 5 min at a frame rate of one frame per 15 sec. Thereafter, a SPECT study was acquired 10 min after injection with a 6° stepwise rotation for 360° and 30-sec acquisition time for each step. Two windows of 20% were set at 73–80 keV and 167 keV. Reconstruction was performed by filtered backprojection employing a Butterworth filter with a cutoff of 0.35.

In phantom studies of a homogenous object, it was found that the application of a 0.2 attenuation correction coefficient resulted in reconstructed slices with a homogenous distribution. Two volunteers were studied employing the Harvard scanning multidetector brain system which was originally manufactured as Cleon 710, whose development has continued. Uniform geometric efficiency may be obtained with this system across the entire slice. Tomographic images were obtained at 2 cm above the orbital meatal line as described elsewhere (*9*).

Intra-Arterial Injection

Following carotid angiography, which was ordered in view of an occipital localized tumor, 2 mCi of [^{201}Tl]DDC was injected into the internal carotid artery of a patient. Slices were made 1.25 cm apart with the Harvard multidetector brain system 30 min after injection.

RESULTS

Thallium-201 DDC Human Brain Uptake

Thallium-201 DDC brain uptake was studied in four normal human volunteers and time-activity curves of cerebral counts were normalized by taking the highest value at 100%. As shown in Figure 1, brain uptake occurred very quickly, reaching a stable count rate 90 sec after injection. In nine patients with acute ischemia of one hemisphere, uptake in the affected side was compared with the other one. No difference was observed in the rate of uptake of the ^{201}Tl uptake between both sides. Lung activity was followed in 11 subjects for 5 min. After 5 min, the activity had fallen to 44.5% ± 10.2 s.d. of the initial peak level.

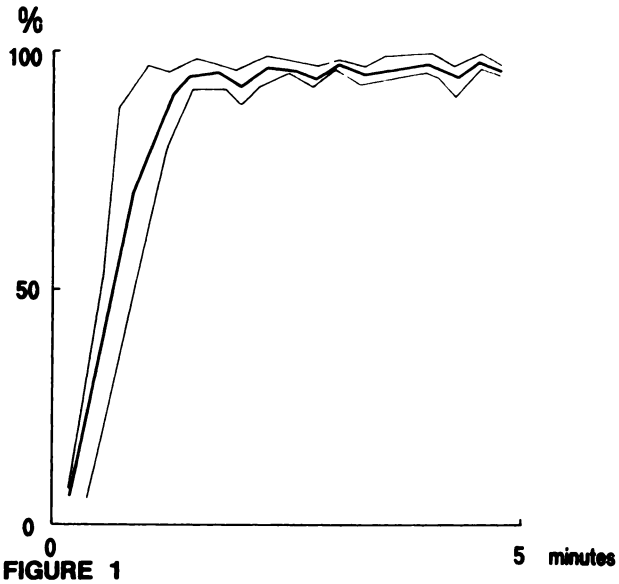

FIGURE 1
[^{201}Tl]DDC brain uptake in four normal human volunteers. Curves were normalized by taking maximum at 100%. Mean ± s.d. is given. Mean = —, s.d. = —.

Whole-Body Distribution

Table 1 summarizes the results of the whole-body measurements 1 hr after injection. Except for the brain, no significant difference was found between [^{201}Tl]DDC and [^{201}Tl]chloride as to its body distribution. The uptake in the brain was increased ~fivefold (4.32% ± 0.6 s.e.m. for [^{201}Tl]DDC versus 0.91% ± 0.07 s.e.m. for [^{201}Tl]chloride). In one normal subject whole-body measurements were performed repeatedly.

Brain uptake was 4.28% 90 min after injection, 4.41% after 3.5 hr, 4.17% after 8 hr, 3.81% after 48 hr, and 3.49% after 72 hr. Assuming a linear decay, a loss of ~0.3% of the initial activity per hour could be calculated.

Normal Human Brain

Figure 2 demonstrates the result obtained by the Harvard multidetector brain system in a normal human brain. There is good demarcation of gray and white matter and basal ganglia. The images after 4 hr suggested no redistribution of the ^{201}Tl after its initial brain uptake.

TABLE 1
[^{201}Tl]DDC and [^{201}Tl]Chloride Whole-Body Distribution as Percentage of Dose (Mean ± s.e.m.)

Organ	[^{201}Tl]DDC (n = 5)	[^{202}Tl]chloride (n = 5)
Brain	4.32 ± 0.60	0.91 ± 0.07
Heart	3.12 ± 0.29	3.05 ± 0.18
Lung	11.01 ± 0.89	11.10 ± 1.09
Liver	8.36 ± 0.83	7.87 ± 0.84
Kidney	5.68 ± 0.59	5.91 ± 0.41
Thyroid	0.84 ± 0.18	0.74 ± 0.15
Salivary gland	0.91 ± 0.19	0.89 ± 0.18

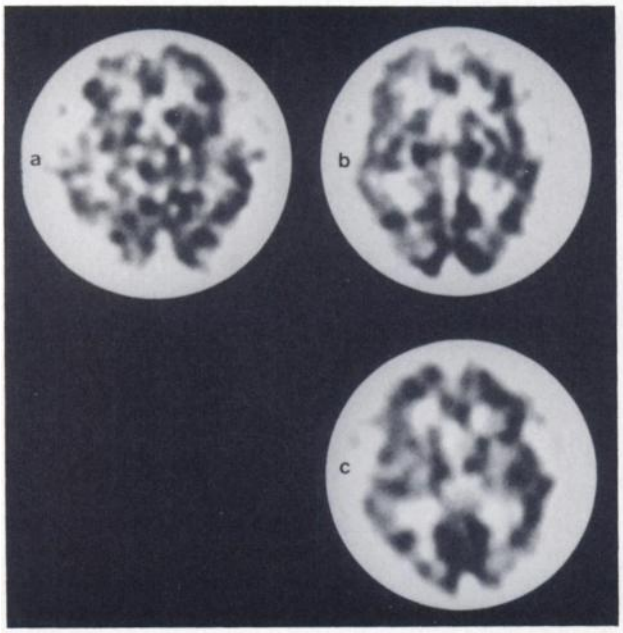

FIGURE 2
Slices obtained by Harvard Multidetector Brain System in normal volunteer 90 sec (a + b) and 4 hr (c) after injection. Slices b and c are at a comparable level through basal ganglia. No redistribution is seen.

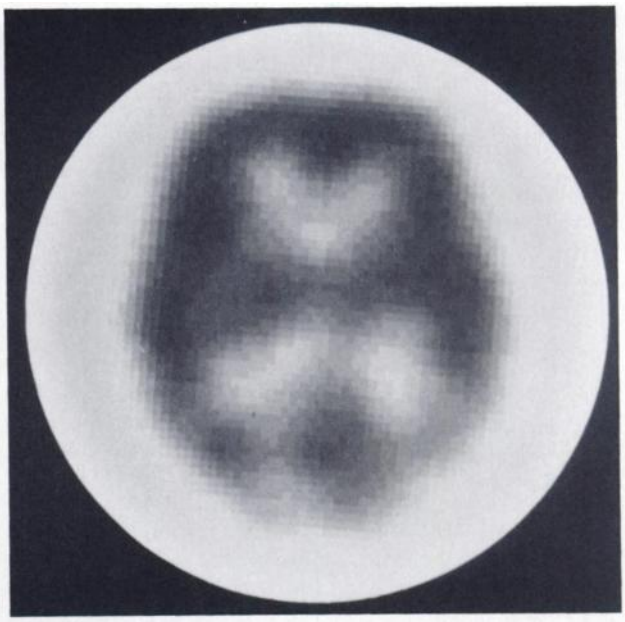

FIGURE 3
Transversal slice of a normal brain (rotating gamma camera).

Figure 3 demonstrates the result obtained in a normal human volunteer employing the rotating gamma camera.

Intra-Arterial Injection

In Figure 4 the images made after injection into the internal carotid artery are given. The distribution area of the anterior and middle cerebral artery are clearly shown. No activity is seen in the rest of the brain proving that the extraction is almost limited to the first passage of the radiopharmaceutical.

Patient Studies

Case 1 (Fig. 5). A 52-yr-old male presented with an acute left-sided hemiparesis and hemihypoaesthesia. The CT showed multiple hypodense areas in the ante-

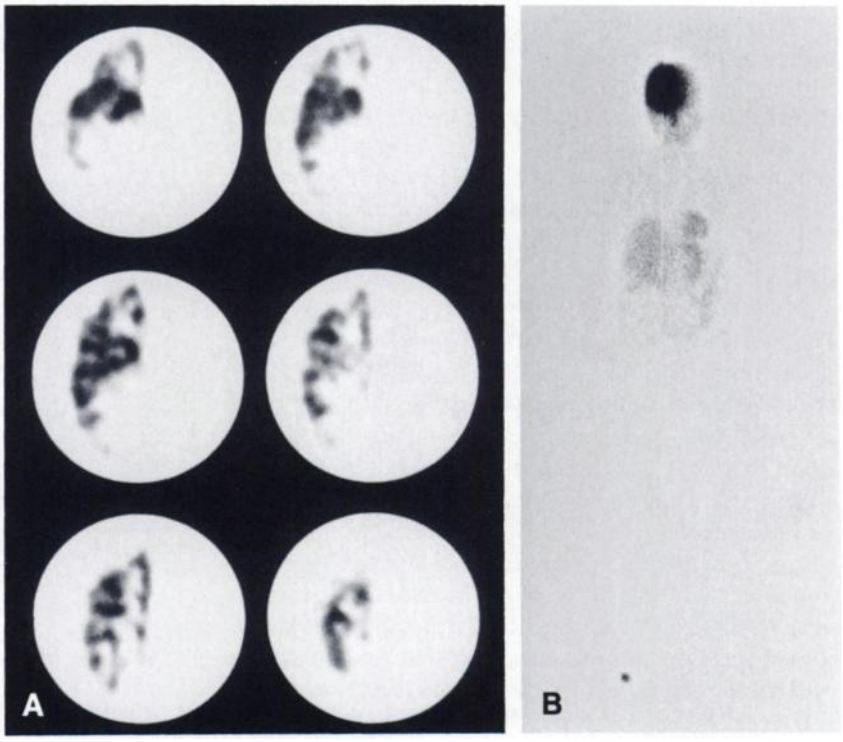

FIGURE 4
A: Transversal slices in same subject (Harvard Multidetector System). 10% background subtraction was performed. Notice absence of activity in the contralateral hemisphere and in the homolateral distribution area of the posterior cerebral artery. B: Whole-body image after intracarotic injection. Note the near absence of activity in the contralateral hemisphere and very low activity in the rest of the body.

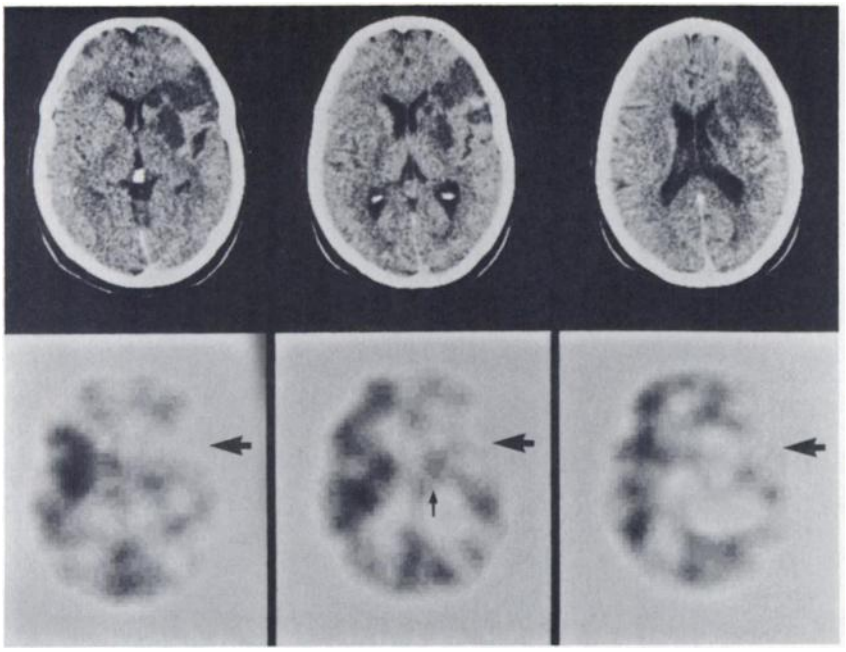

FIGURE 5
Case 1: Multiple hypodense areas are seen in the anterior part of the right middle cerebral artery region on the CT. A larger area with decreased uptake is shown on the SPECT study including the basal ganglia (small arrow) and the entire parietal cortex (large arrows).

rior right middle cerebral artery region. The [^{201}Tl]DDC SPECT study demonstrated a considerably larger area with diminished activity. A marked crossed cerebellar diaschisis was present (not shown).

Case 2 (Fig. 6). A 76-yr-old female was admitted with a progressive stroke. The CT demonstrated initially a small hypodense area lateral to the right ventricle (Fig. 6A), which proved to be much larger after 2 days (Fig. 6B). The SPECT study performed in between showed a large area with diminished activity on the same side with decreased cerebellar activity on the heterolateral side.

Case 3 (Fig. 7). A 89-yr-old female was admitted with a right-sided hemiparesis. The CT showed a hypodense area in the region of the left anterior cerebral artery, while the caudate nucleus was found to be normal. The SPECT study (Harvard Multidetector Brain System) demonstrated diminished activity not only in the anterior area, but also in the head of the caudate nucleus, which is supplied by a branch of the

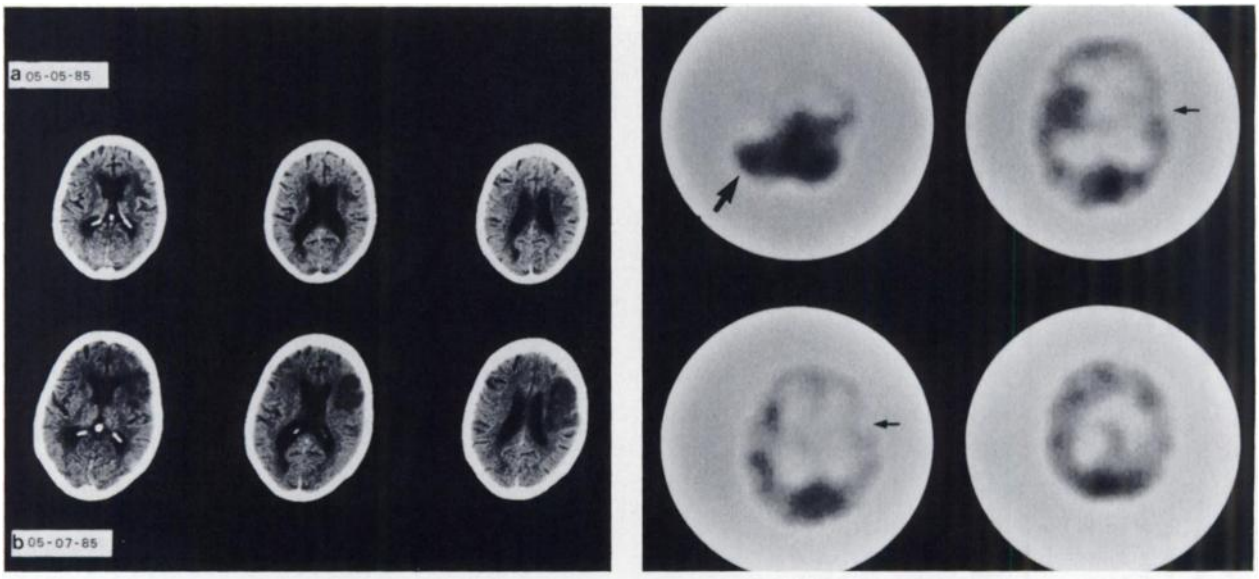

FIGURE 6
Case 2: (left): CT made at admission (a) shows a slight right parietal localized hypodensity. Two days later (b) the size of the hypodense area is increased. (right): The SPECT images, made on the day between the two CT-studies, reveals a large area of decreased uptake both in the basal ganglia and in the parietal cortical area (small arrows). A diminished uptake in the contralateral cerebellar hemisphere is seen: crossed cerebellar diaschisis (large arrow).

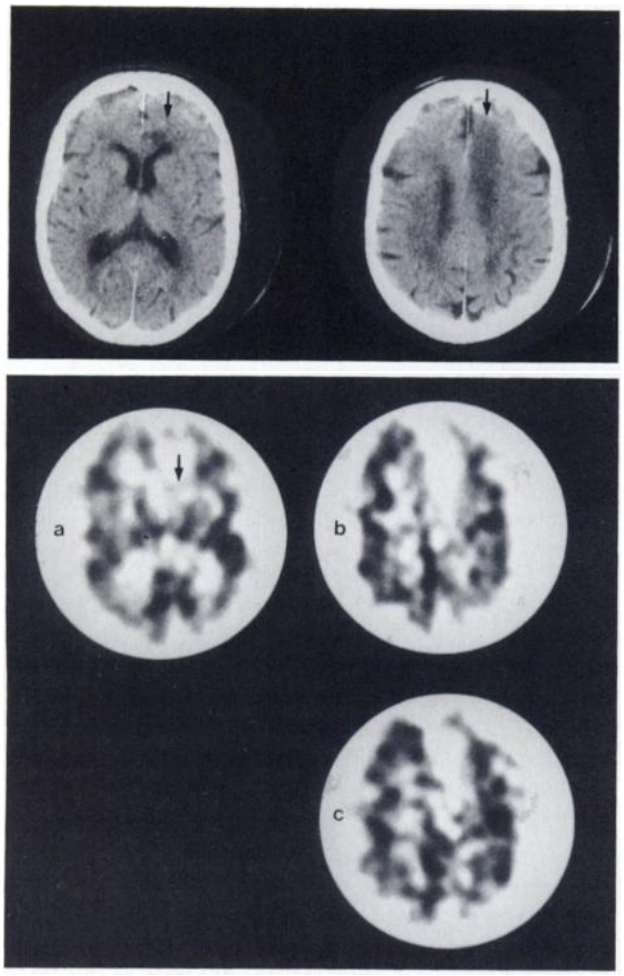

FIGURE 7
Case 3: CT study (top) shows hypodense areas in the region of the left anterior cerebral artery (arrows). Head of the caudate nucleus is normal. The images (below) made with the Harvard Multidetector Brain System (a + b) reveal larger areas with decreased uptake in comparison to the CT study including the head of the caudate nucleus (arrow). The study was repeated 4 hr (arrow) after injection and no redistribution is seen in the infarcted area (c).

anterior cerebral artery. No redistribution of activity in the infarcted area was seen on a study repeated after 4 hr (Fig. 7C).

DISCUSSION

The uptake of [^{201}Tl]DDC in the human brain proved to be as rapid as we found previously in the rabbit (*8*). Equilibrium is reached rapidly, ~90 sec after injection. Thereafter, the amount of activity present in the brain remains extremely stable. The uptake velocity and retention in the brain are clearly superior to N-isopropyl p-iodine-123-iodoamphetamine ([^{123}I]IMP) which reaches equilibrium not before 10 min after injection, while considerable washout occurs between 1 and 24 hr (*10*). The lung clearance of [^{201}Tl]DDC is considerably faster than that of [^{123}I]IMP; Holman et al. (*10*) reported a clearance at 30 min after injection which ranged from 34.6–65.2% of the initial peak activity, while we found for [^{201}Tl]DDC a fall to 44.5% ± 10.2 s.d. 5 min after injection. Also, the total amount of lung activity is considerably lower for [^{201}Tl]DDC. After 1 hr we found 11% ± 2.0 s.d. of the dose in the lung. For [^{123}I]IMP this percentage may be close to 50% as may be derived from the data of Kuhl et al. (*11*). The large pool of lung activity of [^{123}I]IMP which shows considerable washout during the first hours after injection may influence brain uptake and distribution since polar and nonpolar metabolites are released. In fact, cerebral [^{123}I]IMP uptake and distribution represent regional cerebral blood flow only during the first 30 min after injection (*12*).

What is the mechanism of the brain uptake of [^{201}Tl]DDC? The whole-body distribution of [^{201}Tl]DDC proved to be equal to [^{201}Tl]chloride apart from the brain. After the first brain passage virtually no further uptake of [^{201}Tl]DDC was observed. Possibly the [^{201}Tl]DDC complex falls quickly apart in vivo and distributes as the ^{201}Tl-ion. In that hypothesis, the DDC molecule just serves as a carrier which enables the ^{201}Tl by the lipophilicity of the complex to cross the blood-brain-barrier once. At present, we do not know if the distribution within the brain occurs as ^{201}Tl ion or [^{201}Tl]DDC and to which structures it is bound.

The very high extraction rate and almost absence of redistribution render [^{201}Tl]DDC, apart from its photon energy and physical half-life, a superior radiopharmaceutical for the study of cerebral blood flow (CBF). This has been confirmed by high precision digital quantitative autoradiographic techniques in the rat by Lear et al. (*13*). In a comparative study on [^{14}C]iodoantipyrine, [^{123}I]IMP and [^{201}Tl]DDC they concluded that [^{201}Tl]DDC is an accurate radiopharmaceutical for local CBF measurements. Another argument that [^{201}Tl]DDC seems to be a "chemical microsphere" is put forward by our finding that uptake kinetics are the same for ischemic and nonischemic tissues, which differ only as to the total uptake of activity.

Sodium DDC is a known pharmaceutical agent with a low toxicity which is metabolized quickly in vivo to known compounds (*14*). The toxicity of the [^{201}Tl]DDC complex must be low, as both components are used in low amounts compared with the LD50 which is a factor 10 lower for thallium and more than a factor 10 lower for DDC (*14*). The absence of redistribution is important in clinical studies on acute stroke and other acute conditions like epilepsy. From our experience, the imaging may be postponed up to 24 hr after the injection in the acute phase.

Clinical studies on the use of [^{201}Tl]DDC SPECT in various clinical disorders like acute stroke, dementia, and malignancy are now in progress. At this time over

80 patients have been studied without any untoward effect. The presented clinical cases demonstrated that both with the rotating gamma camera and the multidetector system cerebral perfusion defects are easily detected. With the latter, superior images are obtained but image quality of the former may further gain by the use of a slant hole collimator, which reduces the radius of rotation.

Recently, technetium-99m hexamethylpropyleneamine oxime (^{99m}Tc-HM-PAO) has been introduced as a new radiopharmaceutical for SPECT imaging of cerebral blood flow (*15,16*). Knowledge of its uptake mechanism and toxicity is limited at present. A comparative study on [^{201}Tl]DDC and ^{99m}Tc-HM-PAO distribution and redistribution in ischemic brain disease is now in progress.

NOTES

*Merck, Darmstadt, West Germany.

†Omega 500, Technicare Corp., Cleveland, OH.

ACKNOWLEDGMENTS

The authors thank Hannie Bijl and Ellinor Busemann-Sokole for their skillful help with the rotating gamma camera studies; Paul Kazoulis for his expert help with the multidetector system; Bart van Herk for the calculation of the uptake curves; and Josina Brouwer for her secretarial assistance.

Dr. de Bruïne was supported by a grant from Mallinckrodt. Thallium-201 chloride has been supplied as a gift by Mallinckrodt and Dupont/NEN Grant Number CG 85006.

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