Thallium-201 Diethyldithiocarbamate: An Alternative to Iodine-123 *N*-Isopropyl-p-Iodoamphetamine

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The study of cerebral blood flow by single photon emission computed tomography (SPECT) requires lipophilic radiopharmaceuticals. The high cost and limited availability of *N*-isopropyl-p-[I-123]-iodoamphetamine ([^{123}I]IMP) led us to search for alternatives. Following our recent development of thallium-201 diethyldithiocarbamate ([^{201}Tl]DDC), we have compared the brain uptake of [^{123}I]IMP and [^{201}Tl]DDC in rabbits. The brain bound 1.14 ± 0.28% (s.e.m.) of the dose of the injected [^{123}I]IMP and 1.46 ± 0.28% of the [^{201}Tl]DDC. Brain activity of [^{201}Tl]DDC remained stable from 1.5 min after injection up to at least 1 hr. The [^{201}Tl]DDC uptake was more instantaneous than that of [^{123}I]IMP. The ratios of gray to white matter distribution were about equal: 1.41 for [^{123}I]IMP and 1.44 for [^{201}Tl]DDC. The lungs retained 8.32% of the dose of [^{123}I]IMP and only 0.53% of the [^{201}Tl]DDC. In brain macroautoradiography [^{201}Tl]DDC yielded images of good quality with excellent demarcation of gray and white matter, persisting for at least 45 min after injection. We conclude that [^{123}I]IMP and [^{201}Tl]DDC are equally suitable for blood flow study of the rabbit brain. The first human tomographic results obtained in two healthy volunteers demonstrate that clinical application of SPECT [^{201}Tl]DDC may be feasible.

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Imaging of the regional brain metabolism and perfusion has been made possible by positron emission computer tomography and single photon emission computer tomography (SPECT). The latter may find more clinical application because it employs widely available rotating gamma cameras and does not require a cyclotron on site. However, highly lipophilic radiopharmaceuticals are needed which pass the blood-brain barrier. Winchell *(1,2)* developed *N*-isopropyl-p-[I-123]-iodoamphetamine ([^{123}I]IMP) which has a high extraction rate during the first pass and a constant brain activity between 20 and 60 min after injection *(3)*. Iodine-123 IMP has been studied intensively *(4–10)* but the agent is expensive and not readily available, which restricts its clinical use in the study of acute cerebral ischemia. Recently we developed thallium-201 diethyldithiocarbamate ([^{201}Tl]DDC), a lipophilic agent which could possibly serve as an alternative to [^{123}I]IMP *(11)*.

A pilot study showed a considerably greater brain uptake of [^{201}Tl]DDC than ^{201}Tl chloride in the rabbit. A study in rats confirmed this finding: Brain uptake of [^{201}Tl]DDC was comparable to that described for [^{123}I]IMP *(1)*. In rats the percentage of the injected dose per gram wet tissue was 2.73% for [^{201}Tl]DDC 1 hr after injection, whereas Winchell found 2.14% for [^{123}I]IMP. In the following, we compare the results of administering [^{123}I]IMP and [^{201}Tl]DDC in rabbits. We report here the kinetics of brain uptake, the ratio of binding to gray as opposed to white matter, and the distribution of both agents to the main body organs. The favorable properties of [^{201}Tl]DDC prompted us to investigate its use in two human volunteers as a new radiopharmaceutical for SPECT imaging of brain perfusion.

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MATERIALS AND METHODS

Iodine-123 IMP was obtained from "Cygne*." The ^{123}I was cyclotron produced and contaminated with

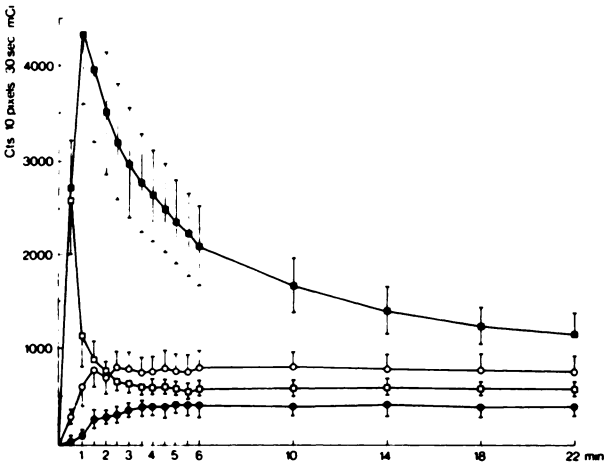

FIGURE 1
[^{123}I]IMP time-activity curves for lung (■) and brain (●) in rabbits (n = 5, mean ± s.e.m.) and [^{201}Tl]DDC time-activity curves for lung (□) and brain (○) in rabbits (n = 6, mean ± s.e.m.), (Φ) s.e.m.

<2.5% Iodine-124 at calibration time. Radiochemical purity was more than 99% and the specific activity was more than 50 Ci/gram [^{123}I]IMP.

The preparation of the ^{201}Tl labeled Tl-Diethyldithiocarbamate ([^{201}Tl]DDC) has been described earlier *(11)*. Sodium Diethyldithiocarbamate† 0.3 H_2O (Na-DDC) of analytical grade was used to make a solution of 1 mg per ml in sterile, pyrogen-free saline. The solution was passed through a 0.2 μm membrane filter and prepared freshly for each experiment. For the studies in human volunteers 2 ml of Na-DDC 5 mg/ml in 0.65% sodium chloride solution was prepared. This solution was sterilized by filtration and kept refrigerated in ampoules. Stability experiments of this preparation were performed. After addition of 100 ml of a copper (II) sulphate solution (10 mg/l) the extinction at 455 nm was measured.

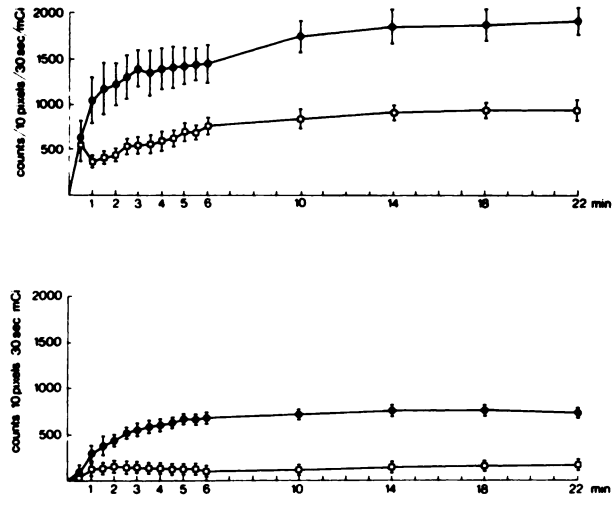

FIGURE 2
Lower: [^{123}I]IMP time-activity curves for liver (□) and kidney (●) in rabbits (n = 5, mean ± s.e.m.). Upper: [^{201}Tl]DDC time-activity curves for liver (□) and kidney (●) in rabbits (n = 6, mean ± s.e.m.); ○ = s.e.m.

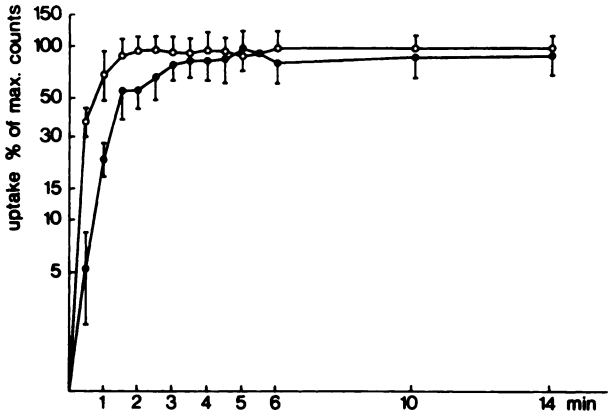

FIGURE 3
Brain time-activity curves for [^{123}I]IMP (○, n = 5) and [^{201}Tl]DDC (●, n = 6) in rabbits (mean ± s.e.m.)

Thallium-201 DDC was prepared by mixing 2 ml of Na-DDC solution containing 10 mg with an equal volume of ^{201}Tl chloride,‡ containing 2-3 mCi. After 10 min incubation at room temperature the radiopharmaceutical was ready for use. The stability of the [^{201}Tl]DDC complex was tested by ascending chromatography using paper strips with n-Heptane and using silica gel impregnated glass fiber ITLC sheets§ with methylethylketone (MEK) as the eluant.

To show the lipophilic properties of the complex, the octanol/water partition coefficient was determined by shaking the chelate in water with octanol. Complexes of Na-DDC with other radionuclides were evaluated. Moreover, chelation with technetium-99m (^{99m}Tc) was attempted using several reducing agents.

Gamma camera studies

Studies were performed using a gamma camera¶ interfaced to a gamma-11 computer (digital). A lower energy general purpose collimator was used. 0.5 mCi [^{201}Tl]DDC (n = 6) or [^{123}I]IMP (n = 5) was injected into an ear vein following anesthesia with 5 mg Fluanison + 0.1 mg Fentanyl/kg. Dynamic studies were performed at a rate of one frame per 10 sec during 22 min. Time-activity curves were obtained for brain, lungs, liver, and kidney after background subtraction.

Tissue distribution studies

Eight rabbits were killed at 25 and 45 min after injection of [^{201}Tl]DDC (n = 4) or [^{123}I]IMP (n = 4) at the end of the gamma camera studies. After the injection of pentobarbital (80 mg/kg), the brain and other organs were removed and weighed. Samples of cortical gray and white matter, basal ganglia, cerebellum, lung, liver, and kidney were weighed and counted in a gamma counter Model CG-4000/PG-4000. Counts were cor-

rected for decay and expressed in percentage of injected dose per gram wet tissue.

Macroautoradiography

A rabbit was given 1.84 mCi [^{201}Tl]DDC and killed after 5 min. Another rabbit received 1.72 mCi and was killed after 45 min. Brains were removed and cut frozen into 20 micron sections on a cryostat. The sections were placed on film (Agfa Osray M3) for 19 hr.

Studies in humans

Three mCi of [^{201}Tl]DDC were injected in two human volunteers. Dynamic images were obtained of the head in a 2-min study of 1 frame per 10 sec on a rotating gamma camera (Omega, Technicare, Inc.) interfaced to a computer (Model MCS-560). A SPECT study was acquired thereafter as follows: A 6° stepwise rotation for 360°, 30 sec acquisition time for each step. Reconstruction of transverse slices was performed by filtered backward projection employing a Butterworth filter with a cut-off of 0.35 after attenuation correction. Whole body images were obtained 3.5 hr after injection with the same gamma camera.

RESULTS

Preparation of [^{201}Tl]DDC

Na-DDC 5 mg/ml in ampoules appeared to be stable for at least 10 wk when kept refrigerated. Degradation products of DDC (diethylamine and carbon disulfide) did not result in a colored complex after addition of copper (II) sulphate. Thallium-201 DDC chelate tested by means of paper chromatography with n-Heptane showed a labeling efficiency of about 80%. This system was not optimal. Drying of the wet spot on the paper resulted in disintegration of the complex whereas omitting of the drying step inhibited the elution process. The silica gel glass fiber sheets employing MEK appeared to be an excellent system. Thallium-201 DDC moves with a flow rate of 80–90, whereas ^{201}Tl chloride remains entirely at the origin.

The labeling efficiency determined with this system was 99% after 10 min, after 5 hr still 97%. The octanol/water coefficient of 88% after one extraction and 96% after the second confirmed the lipophilic property of the chelate. The labeling of [^{201}Tl]DDC with Indium-111 was promising in vitro but accumulated completely in the liver of the rabbit in vivo. Gallium-67 was not tested in vivo as the labeling yield was low. We did not succeed in finding a good reducing agent to obtain a [^{99m}Tc]DDC chelate. Formamidine sulphinic acid (FSA) as described by others *(12)*, did not prove to be successful either. We, therefore, continued our study with [^{201}Tl]DDC. We observed about 6% adsorption of the chelate to the plastic syringe especially to the siliconized plunger in our study. This loss of activity could be reduced to 2–3% by filling the syringe immediately before injection.

TABLE 1
Comparison of In Vivo Distribution of [^{201}Tl]DDC and [^{123}I]IMP in Rabbits*

Item	[^{201}Tl]DDC		[^{123}I]IMP	
	Per organ	Per gram wet tissue	Per organ	Per gram wet tissue
Brain (total)	1.46 ± 0.28	—	1.14 ± 0.18	—
Cerebellum	—	0.18 ± 0.05	—	0.14 ± 0.02
Basal ganglia	—	0.16 ± 0.04	—	0.16± 0.01
White matter	—	0.12 ± 0.03	—	0.13 ± 0.02
Cortical gray matter	—	0.16 ± 0.04	—	0.18 ±0.02
Lungs	0.53 ± 0.17	0.04 ± 0.02	8.32 ± 0.39	0.48 ± 0.11
Liver	14.35 ± 1.85	0.09 ± 0.01	8.68 ± 1.12	0.08 ± 0.01
Kidneys	5.45 ± 1.18	0.29 ± 0.04	5.06 ± 1.99	0.33 ± 0.05

* Expressed as percent uptake of injected dose at 25–45 mins post injection. n = 4; M ± s.e.m.

Gamma camera studies

Time-activity curves for lungs, brain, liver, and kidneys are shown in Figs. 1-2. The brain curve for

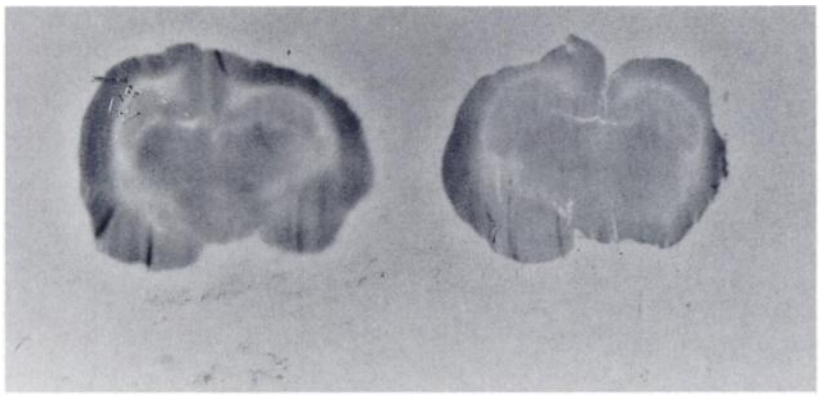

FIGURE 4
[^{201}Tl]DDC macroautoradiograph, rabbit brain, coronal section 5 min (left) and 45 min (right) after injection

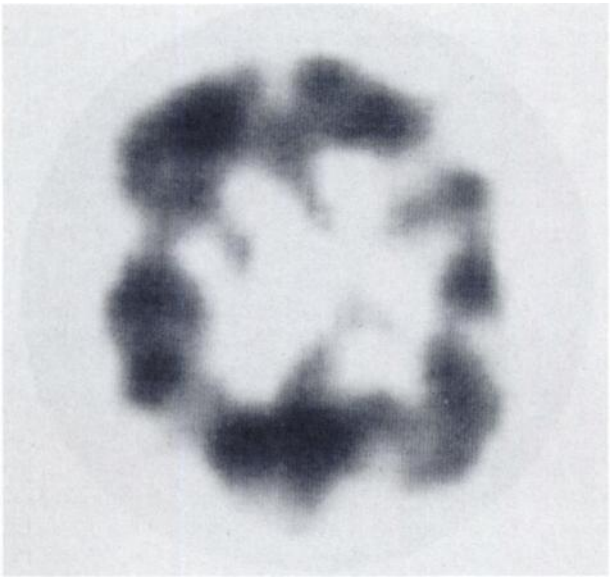

FIGURE 5
Transversal tomograph from human volunteer

[^{123}I]IMP reaches the 90% of maximum level at 3.5 min, while [^{201}Tl]DDC (Fig. 1) reaches this level at 1.5 min. The uptake of [^{201}Tl]DDC is significantly faster, as demonstrated in Fig. 3. Brain activity remains fairly constant after 1.5 min for [^{201}Tl]DDC and after 3.5 min for [^{123}I]IMP. Images taken 1 and 2 hr after injection demonstrated stable brain activity. The lung curve for [^{123}I]IMP reaches its peak at 1 min after injection, whereafter the activity falls down to 30% of maximum at 18 min (Fig. 1). Thallium-201-DDC has a low retention in the lung. The curve reaches its maximum at 0.5 min, whereafter the activity decreases very quickly resulting in a 30% of the maximum level at 2 min after injection (Fig. 1). The [^{123}I]IMP liver curve (Fig. 2) shows a rather rapid uptake in the first 6 min, thereafter liver [^{123}I]IMP activity remains constant. The [^{201}Tl]DDC liver curve demonstrated an increasing activity up to 18 min (Fig. 2).

Iodine-123 IMP uptake in the kidney reaches its maximum at 14 min (Fig. 2). The [^{201}Tl]DDC kidney curve (Fig. 2) shows a rapid uptake after 1 min, followed by a slow increase in activity over the next 21 min.

Tissue distribution

Table 1 demonstrates the uptakes obtained in tissue samples. The percentage brain uptake of the injected dose is about equal for both radiopharmaceuticals (1.14 for [^{123}I]IMP and 1.46 for [^{201}Tl]DDC). The gray/white matter ratio found by the sampling technique proved to be equal for both agents (1.14 ± 0.07 SEM for [^{123}I]IMP and 1.44 ± 0.18 SEM for [^{201}Tl]DDC). The distribution of activity in the lungs for the two radiopharmaceuticals at the time of killing differs markedly: 8.32% of the [^{123}I]IMP dose as opposed to 0.53% of the [^{201}Tl]DDC dose. The activity in the liver is higher for [^{201}Tl]DDC (14.36% of the dose) than for [^{123}I]IMP (8.68% of the dose). The uptake in the kidney is about the same (5.45% for [^{201}Tl]DDC compared to 5.06% for [^{123}I]IMP).

Table 2
Estimated Radiation Dosimetry (in Rads)

Item	[^{201}Tl]DDC (3mCi)	[^{123}I]HIPDM (5mCi)
Whole body	0.63	0.25
Brain	3.9	0.70
Heart	3.9	
Liver	1.89	1.85
Lung	1.35	2.85

Dosimetry

Table 2 shows a comparison of estimated radiation dose to various organs when 3 mCi [^{201}Tl]DDC *(13)* or 5 mCi [^{123}I]HIPDM *(14)* are injected.

Macroautoradiography

The images of the brain section are shown in Fig. 4. A good distinction between gray and white matter is found for both 5 and 45 min images. Possibly some redistribution occurs after 45 min.

Studies in humans

The brain uptake curve during the first 2 min after injection is similar to that found in rabbits—a rapid increase followed by a plateau 1.5 min after injection. The tomographic results obtained in the second volunteer are demonstrated in Fig. 5. White and gray matter differ clearly from each other in the transverse slice. Brain activity remained stable in the two humans studied for at least 2 hr. The whole body image (Fig. 6) demonstrated (apart from an increased brain uptake when compared with ^{201}Tl chloride), a distribution which was quite similar for both agents: marked uptake in salivary glands, thyroid, myocardium, muscles, kidneys, liver, and intestine. In the [^{201}Tl]DDC study, count density over the brain was approximately equal to that found over the heart.

DISCUSSION

Our results show similar brain uptakes, gray to white matter ratios, and macroautoradiographic results for both [^{123}I]IMP and [^{201}Tl]DDC in the rabbit. The retention of [^{123}I]IMP by the lung may explain its slower brain uptake relative to [^{201}Tl]DDC. The faster [^{201}Tl]DDC uptake may yield an even more realistic image of the cerebral blood flow. Holman *(3)*, quoting the work of Rapin et al., described a gray to white

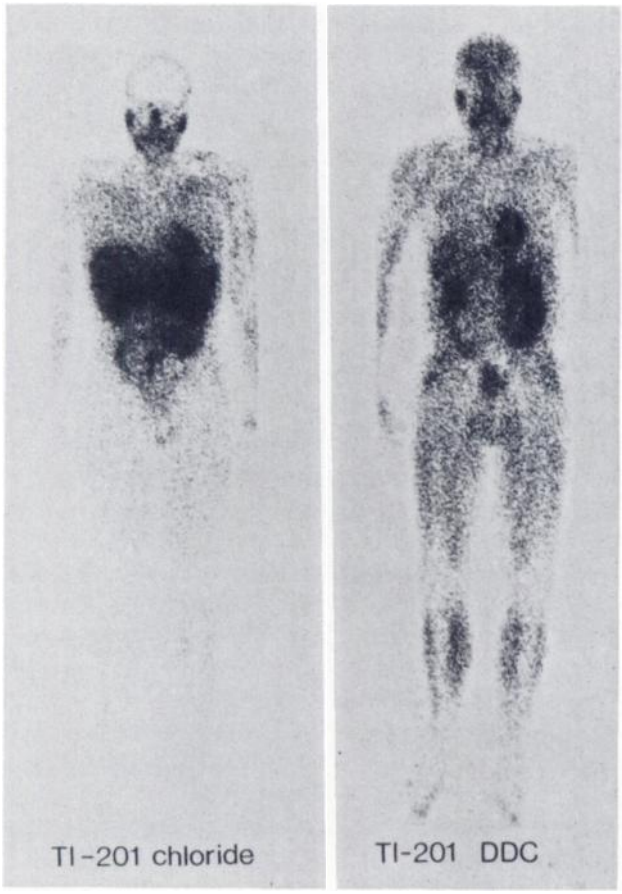

FIGURE 6
Whole-body image of [^{201}Tl]chloride (left) and of [^{201}Tl]DDC (right). Note marked increase in brain uptake

matter ratio of 4.0 for [^{123}I]IMP in rats. This is significantly higher than the 1.41 we found for [^{123}I]IMP and the 1.44 for [^{201}Tl]DDC. However, we obtained this ratio by taking tissue samples, whereas Rapin et al. employed autoradiography. Moreover an interspecies difference may exist. The images we obtained by this technique demonstrated a clear demarcation of white and gray matter with [^{201}Tl]DDC. We were not able to perform quantitative autoradiography.

Single photon emission computed tomography of the brain employing [^{201}Tl]DDC is feasible. Although energy and physical half-life of ^{201}Tl are not ideal, the obtained images with a relatively low activity are encouraging. The radiation dose of 3 mCi of [^{201}Tl]DDC is likely to be higher than that administered by a 5 mCi dose of [^{123}I]IMP or [^{123}I]HIPDM, although the amount of ^{124}I/^{125}I present in the ^{123}I preparation may influence the dose considerably. In Table 2, a tentative radiation dose is given for 3 mCi [^{201}Tl]DDC in comparison to 5 mCi [^{123}I]HIPDM *(13)*. Since the distribution pattern of [^{201}Tl]DDC seems, apart from the brain, to be similar to [^{201}Tl]chloride on whole body images (Fig. 6), we used the data for the latter radiopharmaceutical as given by Samson et al. *(14)*. The brain dose administered by [^{201}Tl]DDC may be similar to the myocardial dose, in view of the comparable count density. However, more work on radiation dosimetry of [^{201}Tl]DDC has to be done.

We conclude that clinical application of [^{201}Tl]DDC for SPECT imaging may become of value in cerebral ischemia, since this agent demonstrates almost instantaneous brain uptake which remains stable for at least 1 to 2 hr.

FOOTNOTES

* Technische Hogeschool, Eindhoven, The Netherlands.
† Merck, Darmstadt, West Germany.
‡ CIL BV, Mallinckrodt, Petten, The Netherlands.
§ ITLC SG, Gelman Sciences, Inc., Ann Arbor, MI.
¶ Maxi Camera 400 autotune ZS, General Electric, Inc.,

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