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Cyclopentadienyl technetium (^{99m}Tc) tricarbonyl piperidine conjugates: biodistribution and imaging studies

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Summary

Synthesis of organometallic complexes of ^{99m}Tc using the precursor ligands *N*-methylpiperidino-4[(bispentahaptocyclopentadienyl)iron] carboxylate and *N*-(isopropyl)-piperidino-4[(bispentahaptocyclopentadienyl)iron]carboxylate is described. The labelling method involved reaction of the ligands with $^{99m}TcO_4^-$ in the presence of $Mn(CO)_5Br$ in dimethyl formamide at 150°C for 1 h in an oil bath. The purification of the complexes was carried out by preparative TLC using ether/*n*-butyl methyl amine (95:5) solvent system. The purified complexes were characterized by HPLC using acetonitrile:water (80:20) solvent system in a PRP-1 column in which both the complexes were eluted as single peaks. Biodistribution studies carried out in rats showed 2.4 ± 0.14 and $1.1 \pm 0.42\%$ of the injected activity in the brain tissue 5 min p.i. for cytectrene I and II,

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respectively. The brain to blood activity ratio was >15:1 for both the complexes at 5 min p.i. Scintigraphic studies in rabbits showed significant uptake of the activity in the brain with fast clearance from blood. The complexes warrant further investigation as agents for brain imaging.

Key Words: technetium-99m; cyclopentadiene technetium carbonyl complexes; cytectrene; receptor imaging agents

Introduction

^{99m}Tc-d,l-HMPAO and ^{99m}Tc-L-L-ECD are the currently used Tc-based radiopharmaceuticals for brain perfusion studies.[1–3] These complexes being lipophilic, cross the blood–brain barrier and are retained in the brain thereby allowing scintigraphic imaging of the brain. Metabolic conversion of the lipophilic complexes to hydrophilic species is believed to be responsible for the retention of the activity in brain.[4] Radiopharmaceuticals that bind to the central nervous system (CNS) receptors *in vivo* are potentially useful for understanding the pathophysiology of a number of neurological and psychiatric disorders. Radiopharmaceuticals based on the cyclotron produced PET isotopes such as ^{11}C, ^{18}F and the SPECT isotope ^{123}I, have already established their role in these studies.[5–9] However, all the above isotopes are cyclotron produced and their availability is limited.

A major part of the diagnostic nuclear medicine is carried out with ^{99m}Tc and hence the development of ^{99m}Tc-based receptor binding radiopharmaceuticals will result in wider availability and use. Labelling of a receptor binding molecule with ^{99m}Tc will involve its modification by addition of a chelating moiety to hold Tc. Structural modification of the receptor binding molecules often results in products with reduced affinity to the receptors.[10–12] A series of neutral and lipophilic ^{99m}Tc complexes, containing *N*-(alkylthiolato)tropane, aminobis(ethylthiolato)tropane, and a TcO^{3+} core, were synthesized and evaluated as CNS dopamine transporter imaging agents.[13–18] ^{99m}Tc-TRODAT-1, in which the chelating moiety bis(aminoethane thiol) is attached to the 2β-position of tropane has shown high affinity, acceptable overall brain uptake ($0.43 \pm 0.16\%$ dose per organ at 2 min p.i.) with good selective uptake in rat striatum. Despite its success in the recent human studies[19–24] it is worthwhile to look for alternate approaches which will give higher uptake in brain.

A new concept for labelling receptor based molecules was developed by Wenzel *et al.* in which Tc^{+} is co-ordinated to cyclopentadienide

($C_5H_5^-$ anion) and three carbonyl carbons to form an organometallic complex.[25–27] These authors have made ^{99m}Tc complexes starting with ferrocene carboxylate derivatives conjugated to receptor specific ligands in the presence of a carbonyl donor. Despite the good results shown by these compounds in biodistribution studies, imaging studies were not reported.

The tricarbonyl cyclopentadienide concept is novel in that it is capable of giving very small molecular weight bifunctional chelating agents (BFCAs) and hence this chemistry is worth exploring. Katzenellenbogen and his group have also demonstrated the use of cytectrene complexes as BFCAs.[28–30] In the present studies, we have attempted to synthesize cyclopentadienyl technetium tricarbonyl conjugates of two piperidine analogs which were reported by Wenzel *et al.* and used them for biodistribution studies in rats as well as for imaging studies in rabbits. The ferrocene-based precursor ligands, I and II, used in these studies and the proposed structure of the corresponding Tc complexes formed[25,27] are shown in Figure 1. Imaging studies with ^{99m}Tc-d,l-HMPAO, was also performed to compare the brain uptake of the present complexes with ^{99m}Tc-d,l-HMPAO.

Materials and methods

$Mn_2(CO)_{10}$, dimethyl formamide, *n*-butylmethylamine and Baker flex TLC plates (20 cm × 20 cm, 0.2 mm coating thickness) were purchased

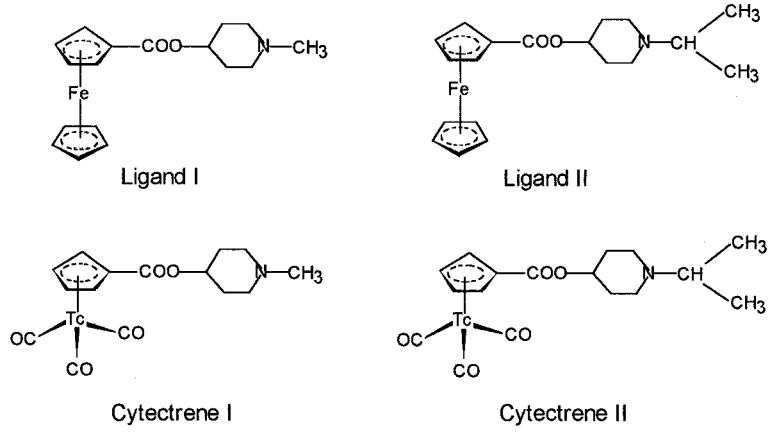


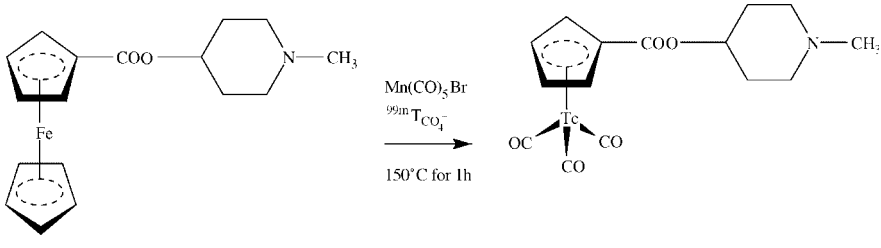
Figure 1. Ferrocene derivatives used for complexation and proposed structure of the corresponding cytectrene complexes

from Aldrich Chemical Company, USA. Flexible silica gel plates with plastic base (IB-F, 7.5×2.5 cm, coating thickness 0.25 mm) were obtained from J.T. Baker Chemical Company, NJ, USA $^{99m}TcO_4^-$ was eluted from a ^{99}Mo–^{99m}Tc alumina column generator or from a solvent extraction generator using MEK as solvent.

The ligands *N*-methylpiperidino-4[(bispentahaptocyclopentadienyl) iron] carboxylate (Ligand I) and *N*-(isopropyl-piperidino-4[(bispentahaptocyclopentadienyl) iron] carboxylate (Ligand II) were synthesized as per the reported procedure.[27] $Mn(CO)_5Br$ was prepared by brominating $Mn_2(CO)_{10}$ in hexane.

Radiochemical studies

Synthesis of N-methylpiperidino-4[(pentahaptocyclopentadienyl)technetium-99m–tricarbonyl]carboxylate (cytectrene I) and N-(isopropyl)-piperidino-4[(pentahaptocyclopentadienyl)technetium-99m–tricarbonyl]-carboxylate (cytectrene II). Ferrocene carboxylate derivatives of 4-hydroxy *N*-methyl piperidine and 4-hydroxy *N*-isopropyl piperidine were used for the synthesis of cytectrene I and II, respectively. Synthetic procedure for the preparation of the complexes is given in Scheme 1. Generator eluted $^{99m}TcO_4^-$ was directly reduced by the ligands in the presence of the carbonyl donor $Mn(CO)_5Br$ to give the respective Tc complexes. 6 mg of the ligand (ferrocene derivative) and 3 mg of $Mn(CO)_5Br$ were dissolved in 0.3 ml of dimethyl formamide in a 5 ml serum vial. 0.3 ml $^{99m}TcO_4^-$ ($\sim$1.1 GBq) in saline was added and the vial was closed with a rubber stopper. A 26 gauge needle was plunged through the rubber closure and the serum vial was suspended in an oil bath maintained at 150°C. The water associated with the reaction mixture escaped as steam through the needle in the initial part of the



Scheme 1.

reaction. After 1 h, the reaction mixture was cooled to room temperature.

Purification

Purification of the reaction mixture was performed using preparative TLC wherein the entire reaction mixture was carefully spotted on a preparative silica gel TLC plate (20 cm × 20 cm, Baker Flex, 0.2 mm coating thickness) marked very carefully at 2 cm from one end. The air-dried plate was developed in 5% *n*-butylmethylamine in ether. The solvent front was allowed to migrate till it reached about 50% of the height of the plate. The plate was removed and allowed to dry in air. A well-defined yellow band was observed at $R_f \sim 0.5$ which was identified to be the product along with the manganese analog, if formed, and the starting ligand. The yellow band was carefully scraped out by using a spatula. A 1 ml capacity polystyrene conical shaped tip was packed with small amount of non-absorbent cotton and this was used as the column. Scraped silica gel was loaded on it and the product was extracted from the silica gel using 2 ml ethanol and the extract was dried under N_2. The contents were reconstituted in 1 ml of saline with 20% ethanol. The purified product was further characterized by TLC and HPLC.

The radiochemical purity of the tracers was estimated by thin layer chromatography using plastic backed flexible silica gel plates (IB-F, 7.5 × 2.5 cm, coating thickness 0.25 mm). 2 µl aliquot of the reaction mixture was spotted 1 cm from the lower end of the plate. The strips were developed using ether:*n*-butylmethylamine (95:5) solvent system. After drying, the plates were cut into seven equal segments and measured for radioactivity in a NaI (Tl) well counter.

Quality control of the complexes

A Waters dual pump HPLC unit with a PRP-1 reverse phase column was used for radiochromatography. The solvent used was a mixture of acetonitrile and water (80:20). The flow rate was adjusted to 1 ml/min. The column was first washed with the solvent for about 10 min prior to injecting the activity. 10 µl of the tracer was injected and the radioactivity of the eluent was monitored.

Biodistribution studies

Male Wistar rats weighing 200–250 g were injected through tail vein with 0.1–0.2 ml of the complex containing 10–15 µCi

(0.37–0.55 MBq) of activity. Animals were sacrificed at 1, 5 and 20 min post-injections. Major organs and tissues were excised, weighed and the radioactivity was measured in a scintillation (NaI–Tl) counter with flat geometry. The per cent injected dose in each organ was calculated from the above data. The per cent injected dose in blood was calculated by measuring the activity in the blood withdrawn by cardiac puncture immediately after sacrifice and assuming the whole blood as 7% of the body weight.

Scintigraphic studies

Scintigraphic studies were done in adult rabbits weighing 3–4 kg. 111–185 MBq (3–5 mCi) of the purified complex (cytectrene I or cytectrene II) was injected intravenously through a penile vein. Serial scintigrams were obtained up to 45 min post-injection using a Picker dual head gamma camera system using a high resolution collimator. All the images were acquired in isotime of 120 s using a 512×512 matrix with an acquisition zoom of 2.

^{99m}Tc-d,l-HMPAO studies

^{99m}Tc-d,l-HMPAO was prepared using *in house* synthesized d,l-HMPAO of isomeric purity greater than 95%.[31] In the protocol followed, 2 mg of d,l-HMPAO was dissolved in 0.1 ml of methanol. To this, 0.5 ml of 0.5 M $NaHCO_3$ buffer (pH 9), 4.2 ml of $^{99m}TcO_4^-$ (15 mCi, 555 MBq) were added in a 10 ml vial. 0.2 ml of saturated solution of stannous tartrate was added as the reducing agent and the contents mixed well. The RC purity of ^{99m}Tc-d,l-HMPAO as determined by reported[31] quality control techniques was $>95\%$ and showed $>90\%$ extraction into $CHCl_3$. Scintigraphic studies were carried out within 5 min of preparation by injecting about 2 ml ($\sim$185 MBq) of ^{99m}Tc-d,l-HMPAO in adult rabbits following the method described above.

Results and discussion

Radiochemical studies of cytectrene I and II

In the present studies we have used dimethyl formamide (DMF) as solvent instead of tetrahydrofuran (THF) as reported by Wenzel

et al.[25,27] The low boiling point (65–67°C) of THF is a deterrent in carrying out the reaction at elevated temperature of 150°C. Use of DMF instead of THF allowed carrying out the reaction in a serum vial sealed with a rubber closure. During complexation, some amount of sedimentation was observed in the reaction mixture in which 20–30% of the activity was associated and the sediment was discarded. Thin layer chromatography pattern of the reaction mixture of cytectrene I and II are given in Figure 2(a) and (b), respectively. The activity was found to be distributed in two peaks, one at the point of spotting and the other at $R_f = 0.45$–0.5. The activity at $R_f = 0.45$–0.5 was identified to be the product. About 40–80% of the spotted activity was seen as product for both the compounds. The HPLC patterns of $^{99m}TcO_4^-$, the reaction mixture of Cytectrene I and its TLC purified fraction are given in Figure 3(a), (b) and (c), respectively. The HPLC pattern of the reaction mixture showed the presence of free $^{99m}TcO_4^-$ whereas the purified compound eluted as a single peak. In preparative TLC, the activity distribution was similar to that of the analytical TLC. A yellow colored band was observed at $R_f = 0.45$–0.5. The yellow band observed was a good marker for identifying the location of the complex on preparative TLC. The activity was eluted with ease from the silica gel using ethanol. The recovery of the activity from the silica gel column was $>90\%$. TLC characterization of cytectrene I and II after TLC purification showed single peaks at $R_f = 0.45$–0.5 and the radiochemical purity of the complexes were $>99\%$. The overall yields of the complexes were 20–25% of the starting radioactivity. TLC studies carried out 24 h post-preparation showed identical pattern as that of a fresh material suggesting good stability of the products in aqueous medium. The lipophilicities of the complexes were estimated by determination of their distribution ratio between chloroform and saline. The distribution ratio between $CHCl_3$/saline was 8.6 ± 0.6 and 17 ± 1 for cytectrene I and II, respectively ($n = 3$).

Biodistribution

Results of the biodistribution studies of cytectrene I and II are given in Tables 1 and 2, respectively. Both the complexes showed significant uptake in brain. The brain uptake of cytectrene I was 2.2 ± 0.28, 2.4 ± 0.14 and $1.2 \pm 0.0\%$ corresponding to a per gram tissue uptake of 1.5 ± 0.18, 1.7 ± 0.07 and $0.87 \pm 0.06\%$ at 1, 5 and 20 min, respectively. About 50% of the activity was observed to clear out from the

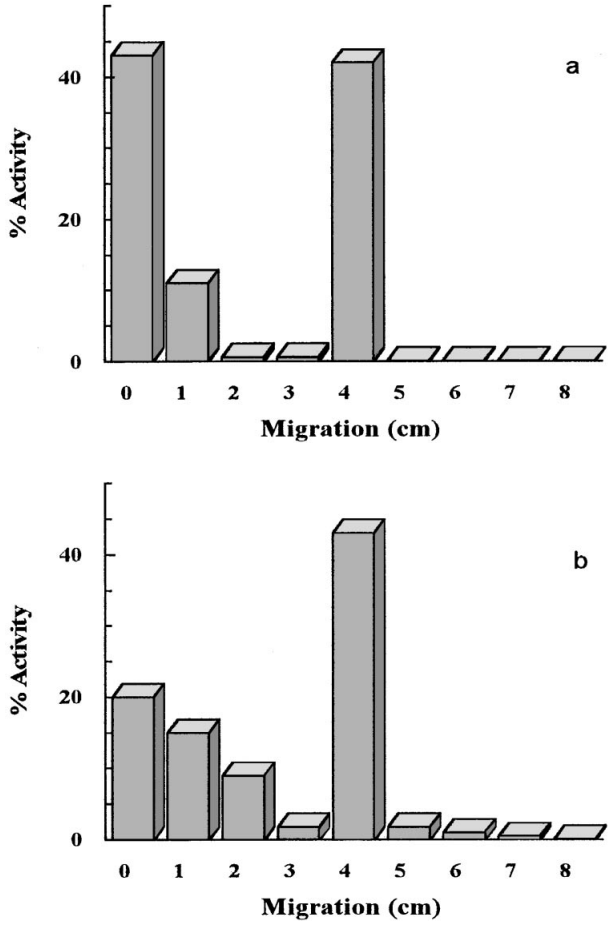


Figure 2. Thin layer chromatography pattern of the reaction mixture of cytectrene I (a) and cytectrene II (b)

brain in 20 min. The total blood activity was 3.2 ± 0.35, 3.0 ± 1.4 and $1.1 \pm 0.07\%$ corresponding to a per gram tissue uptake of 0.17 ± 0.02, 0.11 ± 0.06 and $0.08 \pm 0.01\%$ at 1, 5 and 20 min, respectively. The brain to blood ratios of this complex were 8.8, 15.5 and 11 at 1, 5 and 20 min p.i. 1.4% of the injected activity was observed in the heart at 1 min p.i. and a fast clearance ($\sim 0.3\%$ activity in heart at 20 min) was also observed. The uptake of the complex in the lungs was very high (9.3 ± 2.4, 5.9 ± 0.5 and $2.2 \pm 0.07\%$ of the injected dose at 1, 5 and 20 min, respectively). Excretion of the major activity was through the liver-GIT, though some renal clearance was also observed. Results of the biodistribution studies of cytectrene II is given in Table 2. The

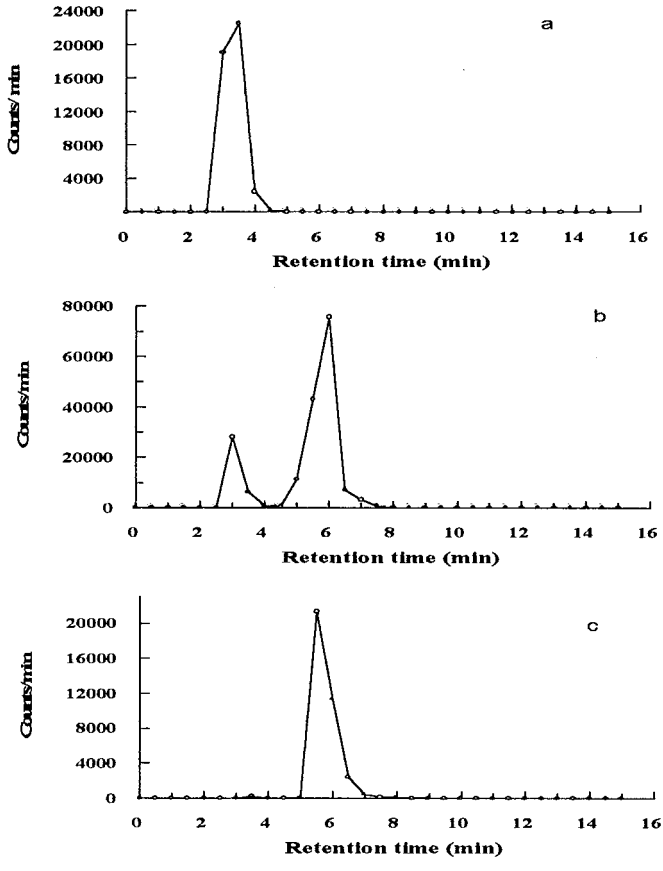


Figure 3. HPLC pattern of $^{99m}TcO_4^-$ (a), reaction mixture of cytectrene I (b), cytectrene I after TLC purification (c). PRP 1 reverse phase column and acetonitrile:water (80:20) solvent system was used for HPLC

biodistribution patterns are similar to that obtained with cytectrene I (see Table 1). The uptake of this complex in brain was less as compared to cytectrene I. However, the brain to blood ratio of this complex at different time intervals appear to be more favorable than that of cytectrene I. Since the actual uptake in brain is lower, cytectrene II may not be superior to cytectrene I for imaging studies. The lung activity of this complex was even higher than that of cytectrene I. As in the case of cytectrene I, this complex also showed predominant excretion through the hepatobiliary system with partial renal clearance. The activity in the stomach for both the complexes was very low suggestive of the absence of $^{99m}TcO_4^-$ impurity in the complex at the time of administration as well as due to *in vivo* degradation of the complex.

Table 1. Results of the bio-distribution studies of cytectrene I in rats[a]

Organ/tissue	% Injected dose at 1 min per		% Injected dose at 5 min per		% Injected dose at 20 min per	
	Organ	Gram	Organ	Gram	Organ	Gram
Brain	2.2 (0.28)	1.5 (0.18)	2.4 (0.14)	1.7 (0.07)	1.2 (0.0)	0.87 (0.06)
Heart	1.4 (0.07)	1.3 (0.14)	0.54 (0.01)	0.7 (0.02)	0.3 (0.05)	0.4 (0.01)
Blood	3.2 (0.35)	0.17 (0.02)	3.0 (1.4)	0.11 (0.06)	1.1 (0.07)	0.08 (0.01)
Kidney	2.2 (0.3)	1.1 (0.14)	5.3 (1.4)	3.0 (1.0)	2.5 (0.28)	1.4 (0.14)
Liver	2.7 (0.7)	0.2 (0.07)	10.1 (1.2)	0.95 (0.02)	26.2 (5.6)	2.6 (0.56)
Gut	4.2 (0.6)	0.17 (0.03)	8.9 (1.5)	0.45 (0.07)	12.5 (0.7)	0.5 (0.07)
Lung	9.3 (2.4)	6.9 (0.07)	5.9 (0.5)	5.3 (0.35)	2.2 (0.07)	1.5 (0.6)
Stomach	0.5 (0.14)	0.26 (0.12)	1.1 (0.4)	0.12 (0.007)	1.7 (0.35)	0.2 (0)
Spleen	0.2 (0.08)	0.35 (0.07)	0.5 (0.07)	0.95 (0.03)	0.45 (0.07)	0.9 (0.14)
Muscle	51.1 (3.2)	0.14 (0.10)	32.0 (5.6)	0.23 (0.11)	16.5 (5.6)	0.1 (0.01)

[a] Values reported are mean (SD) and $n = 3$.

Table 2. Results of the bio-distribution studies of cytectrene II in rats[a]

Organ/tissue	% Injected dose at 1 min per		% Injected dose at 5 min per		% Injected dose at 20 min per	
	Organ	Gram	Organ	Gram	Organ	Gram
Brain	2.0 (0.4)	1.25 (0.13)	1.1 (0.42)	1.2 (0.3)	0.8 (0.11)	0.75 (0.2)
Heart	2.3 (0.15)	1.2 (0.02)	0.7 (0.14)	0.9 (0.1)	0.27 (0.03)	0.47 (0.04)
Blood	2.0 (0.6)	0.1 (0.01)	0.7 (0.3)	0.05 (0.02)	0.75 (0. 3)	0.03 (0.001)
Kidney	2.1 (0.2)	1.0 (0.10)	2.8 (1.2)	2.1 (0.20)	2.5 (0.3)	1.4 (0.20)
Liver	1.1 (0.31)	0.08 (0.001)	4.5 (2.6)	3.00 (2.3)	15.3 (1.4)	1.4 (0.3)
Gut	3.2 (1.2)	0.23 (0.11)	5.1 (4.1)	0.3 (0.2)	11.5 (1.4)	0.7 (0.14)
Lung	15 (1.2)	12.6 (1.30)	5.0 (2.8)	3.0 (1.1)	4.3 (1.0)	1.9 (0.14)
Stomach	1.0 (0.12)	0.20 (0.01)	1.0 (0.6)	0.30 (0.2)	1.9 (0.07)	0.7 (0.14)
Spleen	1.0 (0.08)	1.1 (0.1)	0.4 (0.3)	2.0 (0.5)	1.1 (0.14)	1.8 (0.28)
Muscle	51 (3.1)	0.6 (0.1)	49 (10.0)	0.6 (0.12)	25 (2.8)	0.3 (0.001)

[a] Values reported are mean (SD) and $n = 3$.

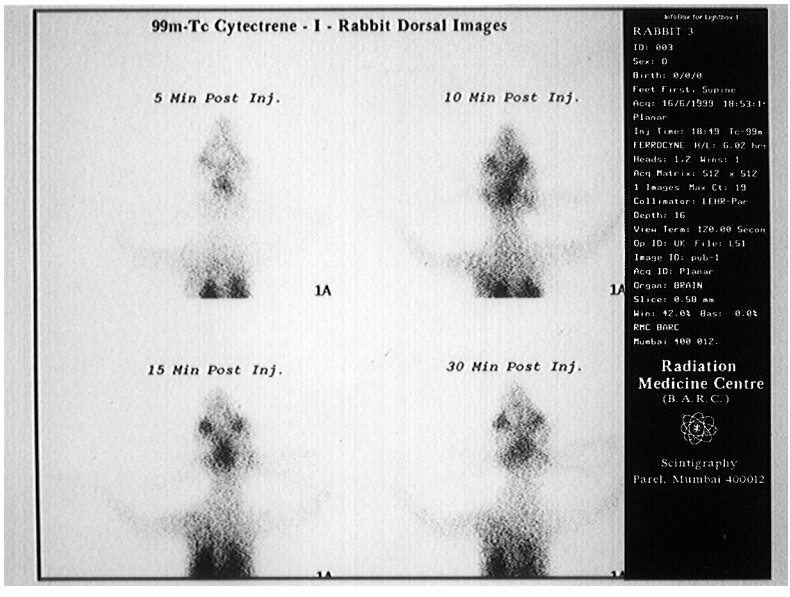


Figure 4. Scintigraphy images of cytectrene I at 5, 10, 15 and 30 min p.i.

Scintigraphy studies

Scintigraphy images of the rabbits injected with cytectrene I and II are given in Figures 4 and 5, respectively. Significant concentration of cytectrene I was observed in the brain of the rabbit. Maximum concentration was observed at about 15 min post-injection. Pharmacokinetic studies showed faster blood clearance and significant target to non-target ratio. Cytectrene II gave identical scintigraphy pattern as that of cytectrene I. The results suggest that cytectrene complexes are capable of penetrating the blood–brain barrier and accumulate in brain. However, in comparison with cytectrene I, the concentration of this tracer in the brain was quantitatively less as seen in the scintigrams. In both the studies, injection through penile vein was preferred as injection in the ear vein caused difficulties in identifying the areas of the tracer concentration in brain. The whole body image of the rabbit showed initial concentration in lungs. Concentration of the activity in the liver was also seen but washing out of the activity from the liver to the gut with time is indicated by the images.

^{99m}Tc-d,l-HMPAO studies

Attempts were made to ascertain the site of concentration of cytectrene I and II by carrying out a comparative imaging study using

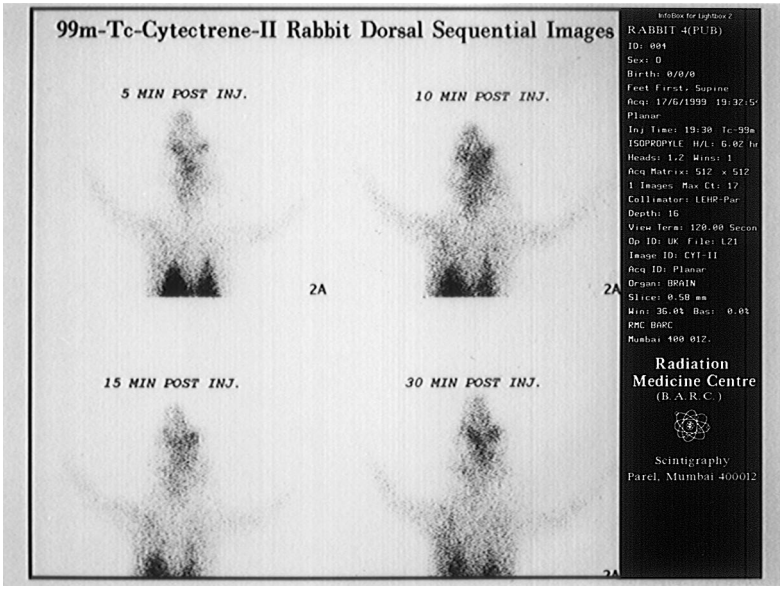


Figure 5. Scintigraphy images of cytectrene II at 5, 10, 15 and 30 min p.i.

^{99m}Tc-d,l-HMPAO. Around 185 MBq (5 mCi) of a freshly prepared ^{99m}Tc-d,l-HMPAO was injected through a penile vein and scintigraphy was carried out using the same camera with identical geometry and acquisition parameters as that used for the earlier study. The scintigrams showed avid concentration of the activity in brain. Figure 6 gives the images with cytectrene I, II and ^{99m}Tc-d,l-HMPAO. Even though the sites of concentration of cytectrene compounds and ^{99m}Tc-d,l-HMPAO were grossly similar, some differentiating features were noticed in the cytectrene scans. In the case of cytectrene compounds, target to non-target ratio was better than that of ^{99m}Tc-d,l-HMPAO. The concentration of ^{99m}Tc-d,l-HMPAO was apparently diffused whereas the concentration of cytectrene was found to be more in the central (medial) part of the brain, with two specific sites behind the optical fossa region of the rabbit brain. However, the identification of the exact deposition pattern of the compound was not possible in the study. An autoradiographic study would furnish some specific data regarding the sites of localization in the brain. The exact structure of the complexes formed could not be ascertained. The complexes are believed to have structures as similar to the one proposed by Wenzel *et al.*[25,26] and Spradau *et al.*[28] A major advantage of this concept is the relatively small size of the bifunctional chelating agent, molecular weight of

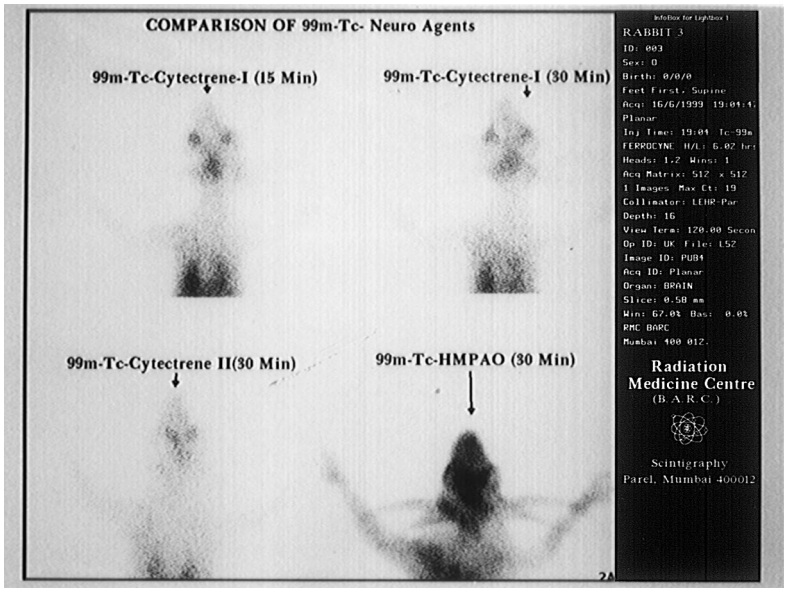


Figure 6. Comparison of the scintigraphy images of cytectrene I and II with ^{99m}Tc-d,l-HMPAO images

252 Da, which includes ^{99m}Tc. Most of the other BFCAs used form Tc complexes, which are of much bigger size. Yet another advantage of this Tc conjugate is that it is possible to separate the complex from the carrier ligand due to its distinct difference in structure. This allows injection of relatively very small number of receptor binding molecules thereby avoiding saturation of receptor sites by the carrier molecules present in the tracer. In most other bifunctional chelating agents, the presence of excess ligand is necessary to keep Tc in the preferred oxidation state. From the present studies, it appears that cyclopentadienyl Tc^{+} tricarbonyl could be used as a carrier molecule for conjugating receptor binding molecules which can be used for imaging the brain.

Conclusion

Synthesis of ^{99m}Tc tricarbonyl complexes using the precursor ligands *N*-methylpiperidino-4[(bispentahaptocyclopentadienyl) iron] carboxylate and *N*-(isopropyl)-piperidino-4[(bispentahaptocyclopentadienyl) iron]-carboxylate and their *in vivo* studies is presented. The complexes were formed in moderate yields. TLC purification could achieve complexes

with high radiochemical purity. Biodistribution studies in Wistar rats revealed significant uptake in brain and high brain to blood ratio. Comparative imaging studies of the complexes with ^{99m}Tc HMPAO in rabbits revealed concentration of the complexes more in the central part of the brain with two specific sites behind the optical fossa while with ^{99m}Tc HMPAO the concentration was apparently diffused.

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