BIOLOGICAL BEHAVIOR OF ^{169}Yb-DTPA AFTER INTRATHECAL ADMINISTRATION

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Ytterbium-169-DTPA has recently been introduced for cerebrospinal fluid studies. Dog experiments were carried out to define the biological behavior and the subacute toxicity of this agent from intrathecal administration. Characteristic disappearance slopes of ^{169}Yb-DTPA in cerebrospinal fluid showed two exponential components with less than 2% retention at 14 days. Cerebrospinal fluid constituents and tissue sections from different regions of the CNS showed no abnormalities during this interval even at concentrations 1,000 times the usual dose, indicating that ^{169}Yb-DTPA is not toxic to the central nervous system.

Radionuclide cisternography and ventriculography have become very useful diagnostic procedures for evaluating cerebrospinal fluid (CSF) circulation and absorption, for demonstrating patency of shunts, and for detecting anatomic abnormalities in specific cases (*1–6*). In the search for a radionuclide agent that fulfills the characteristics of an "ideal" radiopharmaceutical, many have been evaluated. Wagner, et al (7) reported that ^{169}Yb chelated with diethyltriaminepentaacetic acid (^{169}Yb-DTPA) offered many advantages for cisternography. Since the use of ^{169}Yb-DTPA is rapidly gaining acceptance as an important agent for CSF studies, this investigation was undertaken to further define the biological behavior and subacute toxicity of ^{169}Yb-DTPA after intrathecal administration.

MATERIALS AND METHODS

Sterile and pyrogen-free ^{169}Yb-DTPA and saline solutions (3M Co.) were administered to adult dogs weighing 20–30 kg and to immature dogs less than 14 days old. All of the ^{169}Yb-DTPA solutions contained 0.9 mg/ml of ^{169}Yb-DTPA, and two solutions contained nonradioactive Yb-DTPA in concentrations 100 or 1,000 times that of the ^{169}Yb-DTPA. Table 1 summarizes the constituents of each solution.

After intravenous anesthesia with sodium pentothal in adult dogs, each solution was administered into the cisterna magna without barbitage. Only local skin anesthesia with diethylaminoacet-2, 6-xylidide hydrochloride at the site of injection was used in the immature dogs.

Saline control solution was administered to one adult and one immature dog and each of the Yb-DTPA solutions were administered to three adult and three immature dogs. Table 2 summarizes the

TABLE 1. SOLUTIONS ADMINISTERED INTRACISTERNALLY

Component	Saline control (mg/ml)	^{169}Yb-DTPA 1 X (mg/ml)	^{169}Yb-DTPA 100 X (mg/ml)	^{169}Yb-DTPA 1000 X (mg/ml)
^{169}YbNa$_2$-DTPA		0.09	0.09	0.09
YbNa$_2$-DTPA			8.91	89.91
CaNa$_2$-DTPA		0.26	25.7	257.00
Benzyl alcohol	9	9	9	9
Saline	q.s. 1 ml	q.s. 1 ml	q.s. 1 ml	q.s. 1 ml

TABLE 2. DOSE SCHEDULE OF DRUGS ADMINISTERED TO ADULT AND IMMATURE DOGS

Drug	No. of animals	Volume (ml)	^{169}Yb (mCi)	YbNa$_2$-DTPA (mg)	CaNa$_2$-DTPA (mg)
Saline	1 adult	1.0			
	1 immature	0.1			
1 X Yb-DTPA	3 adult	0.3	1.3	0.03	0.08
	3 immature	0.1	0.1	0.01	0.03
100 X Yb-DTPA	3 adult	0.3	1.5	2.6	7.7
	3 immature	0.1	0.1	0.9	2.6
1,000 X Yb-DTPA	3 adult	0.3	1.6	26	77
	3 immature	0.1	0.1	9	26
YbCl$_3$	2 adult	0.25	1.0		

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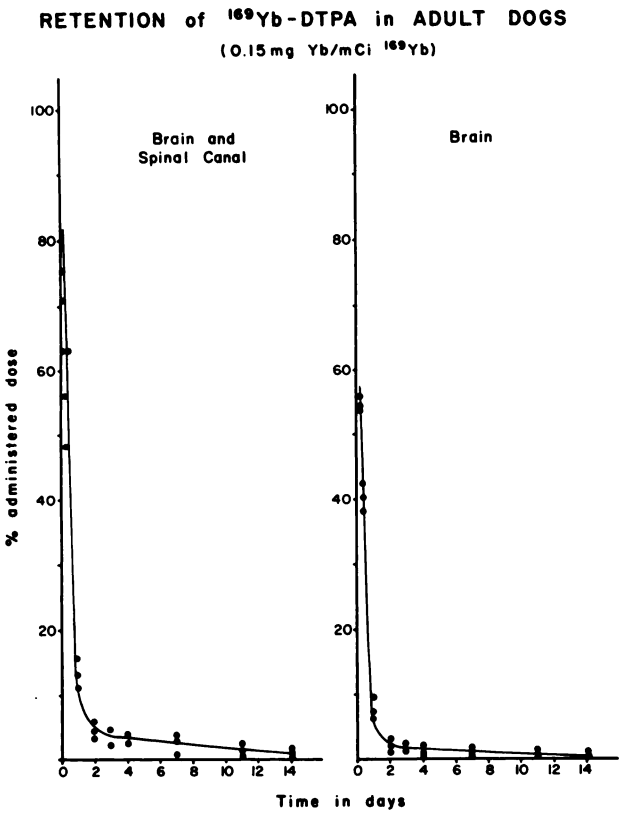

FIG. 1. Comparison of absorption of ^{169}Yb-DTPA from brain only and from brain and spinal canal in adult dogs.

schedule of the doses given to the dogs. In addition, $^{169}YbCl_3$ (1 ×) in saline with 0.9% benzyl alcohol preservative was administered to two adult dogs.

After the intracisternal administration of the solutions, images of the head and entire vertebral canal were made within 30 min after injection, 2–3 and 6 hr, and 1, 2, 3, 4, 6, 8, 10, and 14 days. Images from the Pho/Gamma III camera were recorded on Polaroid and x-ray film, and the data were also stored in PDP 8/I computer. Images of the vertebral canal were performed from the posterior projection and the head from the vertex projection. In the mature dogs the vertebral canal was recorded in 10-in. segments using flexible lead shielding with a 1 × 10-in. open window. The entire head and spine of the puppies were recorded with a single image.

The data stored in the computer from each examination with the Pho/Gamma III were displayed on an oscilloscope. Cursor windows were placed about the areas of interest to eliminate extraneous activity such as from the kidneys or body background. This information was then obtained as printout of activity in a 50 × 50 matrix.

Spinal fluid was withdrawn at the time of initial cisternal puncture and again on the fourteenth day postinjection. These specimens were analyzed for cellular content, glucose, and protein. At the time of injection and at each period of imaging, venous blood was obtained for determination of radioactivity.

Each dog was sacrificed on the fourteenth day after injection by intravascular injection of KCl. Tissue specimens were obtained from multiple regions of the central nervous system, meninges, skull, lung, heart, liver, spleen, kidney, and skeletal muscle. In the immature dogs specimens were obtained also from the femur. These were submitted for measurement of residual radioactivity and for tissue preparation. All tissue preparations were stained with hematoxylin and eosin and examined microscopically.

RESULTS

Adult dogs. CNS retention of ^{169}Yb-DTPA. Immediately after injection, about 40% of the radioactivity was found in the upper part of the vertebral canal and the remainder in the head. Absorption of ^{169}Yb-DTPA from the cerebrospinal fluid appeared to have two exponential components; first, a rapid one with a $T_{1/2}$ of 12–13 hr and an extremely prolonged one with a $T_{1/2}$ of approximately 22–26 days (Fig. 1). During the first exponential phase of absorption there was slightly less retention of Yb-DTPA in those dogs administered the higher concentrations, i.e., the 100 × and 1,000 × solutions of Yb-DTPA. At 24 hr after injection, 20.8% of the 1 × solution, 17.1% of the 100 ×, and 13.7% of the 1,000 × remained within the CNS region (Table 3). The residual amounts had decreased to 3.8%, 1.2%, and 0.8%, respectively, by 14 days

TABLE 3. CNS RETENTION OF ^{169}Yb-DTPA AND $^{169}YbCl_3$ IN ADULT DOGS

	Time post-intrathecal injection						
	0	3 hr	1 day	2 day	3 day	7 day	14 day
1 X Yb-DTPA	100	91.5	20.8	11.3	6.2	5.3	3.8
100 X Yb-DTPA	100	99.5	17.1	5.0	4.3	1.5	1.2
1,000 X Yb-DTPA	100	91.8	13.7	4.2	3.7	1.9	0.8
1 X $YbCl_3$	100	100	99.0	96.5	94.5	92.0	91.0

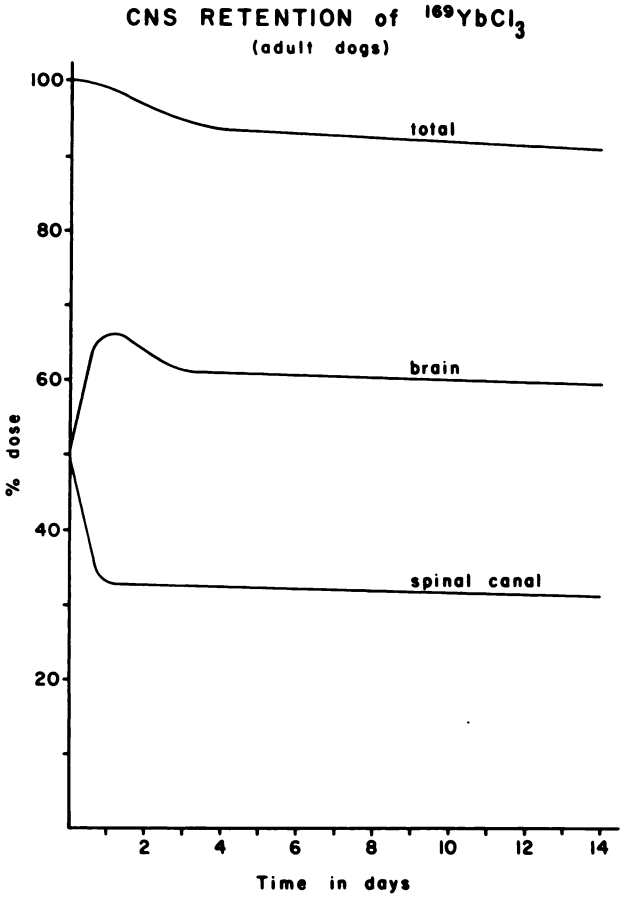

FIG. 2. Absorption of $^{169}YbCl_3$ from intrathecal spaces is very limited and more than 90% of radiopharmaceutical remains in central nervous system.

after injection. The retention of activity in the brain and spinal canal closely paralleled the total CNS retention.

CNS retention of $^{169}YbCl_3$. There was very little absorption of $^{169}YbCl_3$ from the cerebrospinal fluid. Over a period of 2 weeks the activity within the CNS had decreased only 9% (Table 3). Immediately after injection about half of the activity was in the head and the other half in the vertebral canal. Within 24 hr the level in the canal decreased to about 35% and then remained stable (Fig. 2). The activity increased to a peak in the brain at 24 hr, followed by a decrease of about 5% during the next 48 hr, and then stabilized. The $YbCl_3$ appeared to be fixed within the CNS.

Blood levels of ^{169}Yb-DTPA. The blood level of ^{169}Yb increased rapidly after intracisternal injection, peaking at approximately 6 hr, and then decreased rapidly parallel to the absorption from the cerebrospinal fluid (Fig. 3). Within 3 days after injection the level of activity per milliliter of blood decreased to 1×10^{-7} of the dose. There was no measurable activity after 14 days.

Cerebrospinal fluid. There was no significant change in the cellular content, glucose, or protein of the spinal fluid examined 2 weeks after the cisternal injection of any one of the three concentrations of Yb-DTPA or $YbCl_3$ (Table 4).

Immature dogs. CNS retention of ^{169}Yb-DTPA. Immediately after injection, about 30% of the activity was in the upper part of the vertebral canal and the remainder in the head. Absorption of ^{169}Yb-DTPA again demonstrated two exponential components (Fig. 4). The rapid initial phase had a $T_{1/2}$ of 7–8 hr which was faster in immature dogs than adult animals. The second component had a $T_{1/2}$ of 9–10 days. Again there was slightly less retention of ^{169}Yb-DTPA in those puppies administered the higher concentrations of Yb-DTPA. At 24 hr after injection 10.9% of the 1 × solution, 8.4% of the 100 ×, and 7.3% of the 1,000 × remained within the CNS region (Table 5). The residual amounts had decreased to 1.6%, 1.7%, and 1.4%, respectively, by 14 days after injection. Retention of activity in the brain and spinal canal closely paralleled the total CNS retention.

Adult and immature dogs. Tissue examination. Sections of the CNS included cerebral cortex, basal ganglia with ventricular wall, midbrain and pons with aqueduct, cerebellum, region of 4th ventricle, spinal cord, and meninges. Also included were lung, liver, spleen, kidney, and skeletal muscle. Micro-

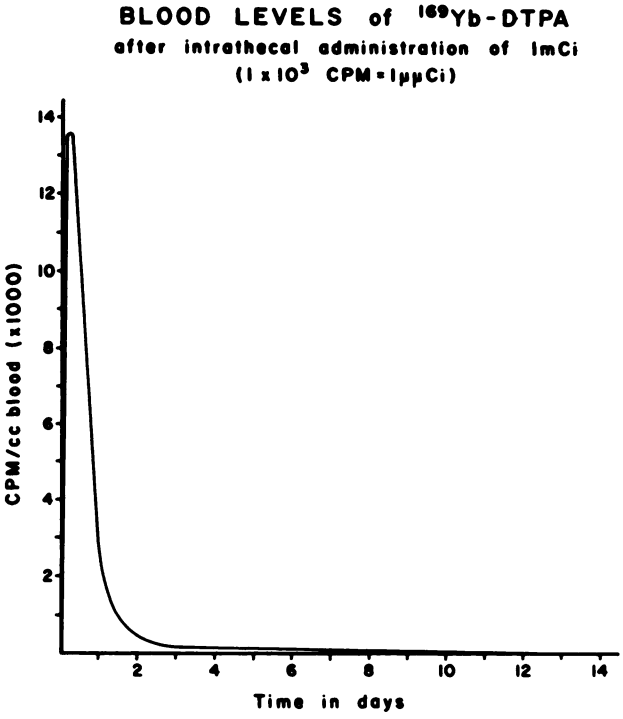

FIG. 3. Blood level of ^{169}Yb-DTPA correlates with absorption of radiopharmaceutical from central nervous system.

TABLE 4. SPINAL FLUID ANALYSIS (ADULT DOGS)

	Pharmaceutical	Time	Gross appearance	Cells (per ml³) Polys	Lymphs	RBCs	Chemistries (mg%) Protein	Glucose
Dog 1	Saline	pre-	Clear	0	0	3	26	78
		post-	Clear	0	0	0	23	84
Dog 2	1,000 X Yb-DTPA	pre-	Bloody	51	29	37,000	36	95
		post-	Clear	0	4	12	22	85
Dog 3	1,000 X Yb-DTPA	pre-	Bloody	41	8	16,800	—	95
		post-	Clear	0	2	0	21	80
Dog 4	100 X Yb-DTPA	pre-	Clear	0	2	0	18	85
		post-	Clear	0	1	2	20	80
Dog 5	1,000 X Yb-DTPA	pre-	Clear	0	0	3	18	95
		post-	Clear	0	3	0	14	90
Dog 6	100 X Yb-DTPA	pre-	Clear	0	0	0	20	80
		post-	Clear	0	0	0	18	75
Dog 7	100 X Yb-DTPA	pre-	Clear	0	0	0	12	55
		post-	Clear	0	0	15	28	95
Dog 8	1 X Yb-DTPA	pre-	Bloody	5	0	13,000	11	105
		post-	Clear	0	0	15	14	95
Dog 9	1 X Yb-DTPA	pre-	Clear	0	0	0	12	105
		post-	Hazy	0	3	1,640	22	80
Dog 10	1 X Yb-DTPA	pre-	Clear	0	0	0	18	110
		post-	Clear	0	0	0	14	90
Dog 11	1 X $YbCl_3$	pre-	Clear	0	2	0	17	85
		post-	Clear	0	0	0	21	80
Dog 12	1 X $YbCl_3$	pre-	Clear	0	4	15	24	95
		post-	Clear	0	0	0	20	85

1 X = 0.0015 mg Yb; 100 X = 0.15 mg Yb; 1,000 X = 1.5 mg Yb.
pre = immediately before intracisternal injection.
post = 14 days after intracisternal injection.

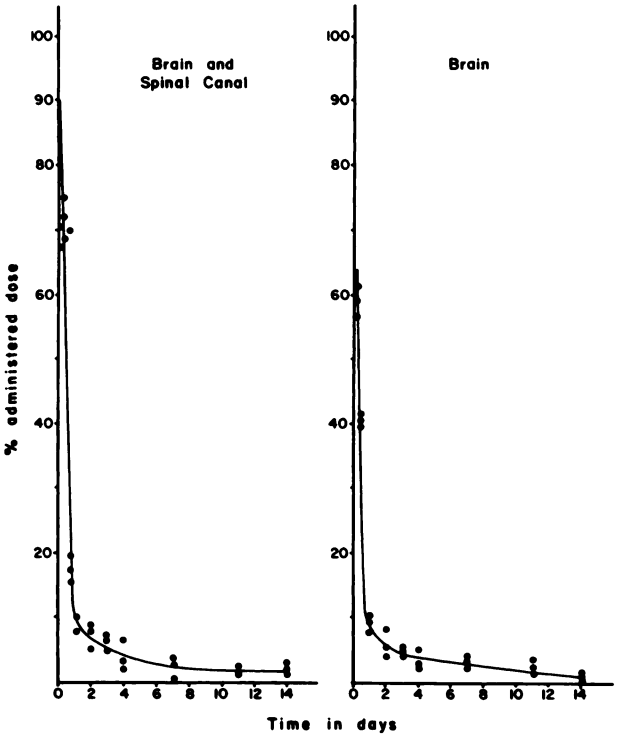

FIG. 4. Comparison of absorption of ^{169}Yb-DTPA from brain only and from brain and spinal canal in immature dogs.

scopic examination did not demonstrate evidence of hemorrhage, inflammation, fibrosis, or vascular reaction.

Tissue distribution of residual activity. Aliquots of tissue from the organs and regions examined microscopically were measured for residual radioactivity. These data were corrected for decay and expressed per gram of wet tissue (Table 6). In the adult dogs the residual activity in the CNS was of the order of 0.8–1.4 $\mu\mu$Ci/gm (mean of wet tissue). Deposition in bone was of the same order as other organs except for the central nervous system.

DISCUSSION

Ytterbium is a rare earth element of the lanthanide group and the radioactive isotope ^{169}Yb is produced by thermal bombardment of enriched ^{168}Yb. The ^{169}Yb-DTPA used in this investigation is prepared by adding $^{169}YbCl_3$ to sterile pentetate trisodium calcium solution. This solution is diluted with five parts water that contains 0.9% sodium chloride and 0.9% benzyl alcohol, and the pH is adjusted to 6.0–7.4 with 0.1 *N* hydrochloric acid or 0.4 *N* sodium hydroxide. After sterilization by filtration, the ^{169}Yb-DTPA solution is transferred to sterilized vials, sealed, and then steam sterilized for 30 min at 120°C. Samples of the solutions are tested for pyro-

TABLE 5. CNS RETENTION OF ^{169}Yb-DTPA IN IMMATURE DOGS

	Time post-intrathecal injection						
	0	1 hr	1 day	2 day	4 day	8 day	14 day
1 X Yb-DTPA	100	90.0	10.9	9.6	5.6	3.6	1.6
100 X Yb-DTPA	100	90.0	8.4	6.9	4.4	2.4	1.7
1,000 X Yb-DTPA	100	88.2	7.3	4.9	3.9	2.7	1.4

TABLE 6. TISSUE DISTRIBUTION OF RESIDUAL ^{169}Yb-DTPA (14 DAYS AFTER INTRACISTERNAL INJECTION)

	^{169}Yb-DTPA (cpm × 10^3/gm tissue)				$^{169}YbCl_3$ (cpm × 10^3/gm tissue)
	Adult dogs		Immature dogs		
	Mean	Range	Mean	Range	
Brain					
Cerebral cortex	1.35	0.39–2.92	0.37	0.22–0.50	33.03
Mid-brain	1.02	0.50–1.99	0.42	0.30–0.57	
Basal ganglia	1.07	0.50–1.45	0.27	0.21–0.33	
Pons	0.82	0.37–1.34	0.54	0.35–0.82	
Cerebellum	1.38	0.60–2.17	0.63	0.31–0.93	
Spinal cord	1.17	0.67–2.06	0.51	0.43–0.67	
Meninges	0.17	0.11–0.28	0.13	0.11–0.21	18.10
Lung	0.15	0.04–0.28	0.17	0.5 –0.27	4.47
Heart	0.20	0.12–0.42	0.25	0.11–0.37	3.60
Liver	0.31	0.18–0.40	0.26	0.14–0.43	7.16
Spleen	0.35	0.27–0.53	0.17	0.11–0.20	7.11
Kidney	0.37	0.23–0.52	0.25	0.21–0.31	3.23
Skeletal muscle	0.26	0.22–0.31	0.21	0.15–0.29	3.41
Skull	0.31	0.17–0.42	0.34	0.25–0.48	4.80
Distal femur			0.21	0.17–0.26	
Femoral shaft			0.17	0.12–0.21	

10^3 cpm = 1 $\mu\mu$Ci ^{169}Yb

genicity in rabbits and sterility in fluid thioglycollate medium according to the methods described in *USP XVIII*.

After absorption from the cerebrospinal fluid, ^{169}Yb-DTPA equilibrates with extracellular fluid and is removed from the blood by glomerular filtration without resorption (*8*). The ^{169}Yb-DTPA is not bound to plasma proteins and is recovered in urine in an unchanged state. Ninety percent is excreted in 24 hr and the biological half-time in blood is 90 min. The final 1% of ^{169}Yb-DTPA has a biological half-time of 6 days.

The biological $T_{1/2}$ in mature dogs was on the order of 14 hr, i.e., 12–13 hr in the intrathecal space and 1½ hr in the extracellular fluid. In puppies younger than 2 weeks old the biological half-life was 9 hr (7–8 hr in the intrathecal space and 1½ hr in the extracellular fluid). The more rapid absorption of ^{169}Yb-DTPA from the CSF in younger animals appears similar to that observed in children instead of adults. Approximately 5% of the intrathecal dose is slowly absorbed from the intrathecal space, but the $T_{1/2}$ of 10 days in puppies is appreciably less than the $T_{1/2}$ in adult dogs of 24 days. With the more concentrated solutions of Yb-DTPA (100 × and 1,000 ×) the residual ^{169}Yb-DTPA in the slow component was only 2–3% of the intrathecal dose. There is a direct relationship between the concentration of a solute and the diffusion rate (*9*) which may account for the smaller residual of ^{169}Yb-DTPA in the slower component.

The necessity of converting all of the $YbCl_3$ to Yb-DTPA is illustrated in Fig. 2. There is a fast and a slow component in the absorption from the intrathecal space. Approximately 7% of the injected dose is absorbed with a $T_{1/2}$ of 1 day, but the remaining 93% is essentially fixed in the brain and meninges. The biological $T_{1/2}$ of the slow component is from 300 to 350 days.

In both adult and immature dogs Yb-DTPA did not produce evidence of biologic damage even at concentrations 1,000 times that of the usual dose. Examination of the cerebrospinal fluid did not suggest any toxic affect on the central nervous system and microscopic examination of organs including the central nervous system was negative. At 2 weeks after

intracisternal injection in adult dogs, residual ^{169}Yb-DTPA in the brain ranged from 0.08 to 0.6 μCi (based on average brain weight of 20–30-kg dogs) which was less than 0.01% of the administered dose. Residual concentrations of ^{169}Yb-DTPA in the brain was as much as ten times that in the meninges which suggests that brain tissue does differentially retain a greater amount of the radiopharmaceutical. Residual concentration in the meninges was similar to that found in other organs. Since these findings do not correlate with the distribution found for $^{169}YbCl_3$, it does not seem probable that the greater residual of ^{169}Yb-DTPA in the brain is due to contamination with $^{169}YbCl_3$.

The data obtained from this investigation indicates that ^{169}Yb-DTPA is nontoxic to the central nervous system.

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