ATTACHMENT 10
FORM FD 1571
3M PROTOCOL MRP 10-

APPENDIX A - PLAN OF INVESTIGATION

Describing A Clinical Evaluation of Ytterbium (Yb 169) DTPA For Cisternography

Clinical Investigator
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Estimated: Starting Date 1JUL74 Completion Date 1JUL75 No Patients 50

SUBJECT SELECTION

Subjects will be patients of the hospital named above, and must require the diagnostic procedure, ie the request that a cisternography study be performed to aid in the diagnosis of the patient's condition. The use of the radiopharmaceutical is contraindicated in pregnant women and persons under the age of 18 years, except in unusual circumstances.

RADIOPHARMACEUTICAL

Sterile, nonpyrogenic solutions of Ytterbium (Yb 169) DTPA for cisternography will be purchased from the 3M Company. The 1.25 ml in each unit dose vial will contain approximately 0.5 mg ytterbium DTPA, 1.25 mg calcium trisodium DTPA, 11.2 mg benzyl alcohol and 2.5 mCi ytterbium 169 on date of assay. The expiration date will be six weeks beyond the date of assay.

EXPERIMENTAL DESIGN AND DATA REPORTING

Ytterbium (Yb 169) DTPA for cisternography will be administered by intrathecal (lumbar) injection in the smallest reasonable dose (0.5-2.0 ml) consistent with the greatest value in terms of relevant diagnostic information for the patient. On forms provided by the 3M Company, the lot number and the administered ytterbium-169 will be recorded for each patient. The quality of images and any comments relating to procedural difficulties will also be recorded. Any indication of an adverse patient response will be reported immediately to the 3M Protocol Coordinator (612/733-7438).

Data reporting forms and a brief summary statement by the investigator will be transmitted semi-annually to the AEC and the 3M Company.

FORM FD 1571

PROTOCOL MRP 10-

Clinical Evaluation of Ytterbium (Yb 169) DTPA

For Cisternography Studies

Patient	Hospital No	Injection Date	Ytterbium (Yb 169) DTPA Lot No	Dose (mCi)	Results of Study Good	Poor
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						

Comments Regarding Procedural Difficulties or Adverse Patient Responses:

Patient	Comments

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APPENDIX B

EXCRETION AND DOSIMETRY

EXCRETION

In clinical trials sponsored by the 3M Company, Ytterbium (Yb 169) DTPA injected into the intraspinal space was found to be excreted in the urine (Table 1). When the percent of the dose retained in the body is plotted against time, a two-component curve is formed (Figure 1). The fast component of elimination has an effective half-time of 8 hours and an initial activity of 60 percent of the administered activity. The slow component of elimination has an effective half-time of 26 hours and an initial activity of 40 percent of the administered activity. Up to 1 percent of the injected dose may be retained or is eliminated with a very long half-time.

DOSIMETRY

Whole Body, Spine and Brain.

1. Assumptions
   - A. The gamma dose-rate constant K for Yb-169 is 1.95 R/hr/mCi at 1 cm. This value was determined by the 3M Nuclear Medical Laboratory (no published value is available).
   - B. The total activity administered is assumed to appear in each organ or tissue of interest at the time of injection. Using this arbitrary conservative assumption, the maximum possible radiation dose to that organ or tissue is determined.
   - C. The activity is homogeneously distributed within the tissue of interest.
   - D. The tissue of interest is that of the "Standard Man."
   - E. A dose estimate can be calculated from Equation (1).

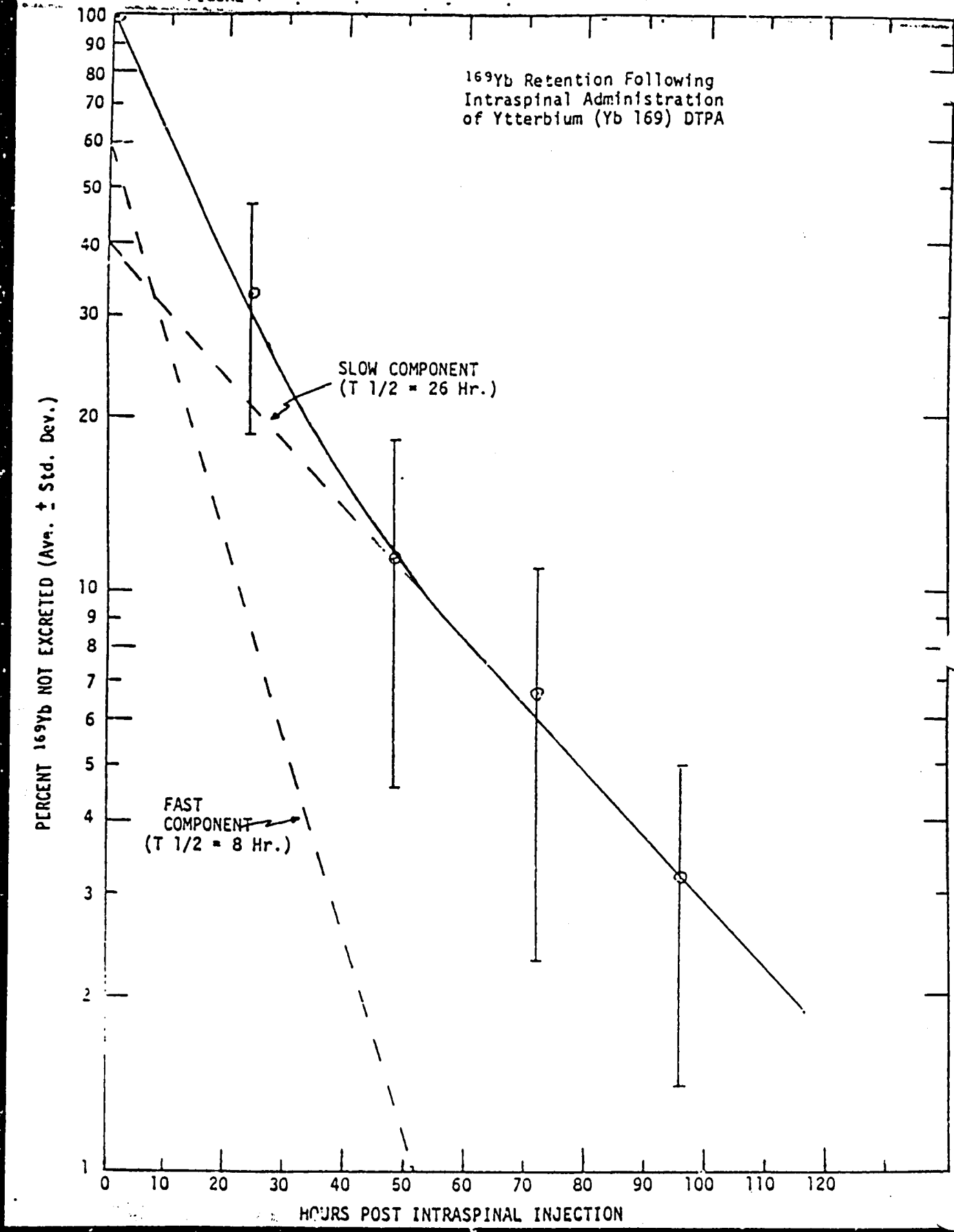
Table 1

Urinary Excretion of Ytterbium (Yb 169) DTPA
Following Intraspinal Administration into Patients

Hours Post Injection	^{169}Yb Urinary Excretion			
	Normal Patients		Cerebral Atrophy	
	Number	% Activity Excreted	Number	% Activity Excreted
24	4	66 (43-86)*	7	68 (58-88)
48	4	90 (79-97)	7	88 (76-95)
72	4	95 (88-98)	6	92 (85-98)
96	4	97 (94-99)	5	96 (95-99)

* Range

FIGURE 1


169Yb Retention Following
Intraspinal Administration
of Ytterbium (Yb 169) DTPA
SLOW COMPONENT
(T 1/2 = 26 Hr.)
FAST
COMPONENT
(T 1/2 = 8 Hr.)
PERCENT 169Yb NOT EXCRETED (Ave. ± Std. Dev.)
HOURS POST INTRASPINAL INJECTION
100
90
80
70
60
50
40
30
20
10
9
8
7
6
5
4
3
2
1
0
10
20
30
40
50
60
70
80
90
100
110
120

Equation (1) Radiation Dose

$$\bar{D} = .0331\ cKgT$$

where: D = average absorbed dose in rads
c = activity concentration in μCi/gm tissue
K = gamma dose-rate constant in R/hr/mCi at 1 cm
g = geometry factor (which is a function of organ size and shape)
T = effective exposure time in days

This method is taken from:

Johns: The Physics of Radiology, pp 563-5 and Hine and Brownell, Radiation Dosimetry, pp 857, 8. All values for g which are used in the calculations are taken from these references.

2. Dose Estimates

A. Whole Body

Assume a mass of 70 kg and g = 125

Then: Fast component dose is 0.023 rads/mCi
Slow " " " 0.051 "
Total Dose 0.074 rads/mCi

B. Spinal Cord

Assume a mass of 30 gm and g = 10

Then: Fast component dose is 4.3 rads/mCi
Slow " " " 9.3 "
Total Dose 14 rads/mCi

C. Brain

Assume a mass of 1500 gm and g = 40

Then: Fast component dose is 0.34 rads/mCi
Slow " " " 0.74 "
Total Dose 1.1 rads/mCi

3. Summary

The following table summarizes the absorbed doses (rads/mCi) for intraspinal administration calculated by Equation (1).

Organ or Tissue	Fast Component	Slow Component	Total Dose
Whole body	0.023	0.051	0.074
Spinal cord	4.3	9.5	14
Brain	0.34	0.74	1.1

DOSIMETRY Kidney, Bladder and Bone

1. Assumptions

A. Ytterbium (Yb 169) DTPA leaving the spinal column enters the blood and can be treated as a slow intravenous injection.

B. In the patient with normal kidney function, 99% of the activity entering the blood stream at any one time is removed from the body by glomerular filtration with an effective half-life of 1.5 hours. The final one percent is removed with an effective half-life of 6 days.

C. In the patient with severely impaired kidney function, the activity entering the blood stream at any one time is removed with a half-life of 24 hours.

D. The dose estimate is calculated from Equation (1).

E. The organ or tissue in question is that of the Standard Man.

2. Dose Estimates

a. Kidney

Assume a mass of 155 gm for each kidney, g = 18, and that the administered activity is homogeneously distributed throughout both kidneys.

a. In the patient with normal kidney function,
Then: Fast component dose is 0.46 rads/mCi
Slow " " " 0.45 "
Total Dose 0.91 rads/mCi

b. In the patient with severe kidney impairment, (elimination with $T_{\frac{1}{2}}$ = 24 hrs) the dose is 7.5 rads/mCi.

B. Bladder

Assume a mass of 147 gm and g = 31, and all of the administered activity is initially in the bladder. Assume the bladder empties at the same rate whether the kidney is impaired or not.

Then: Fast component dose is 0.84 rads/mCi
Slow " " " 0.82 "
Total Dose 1.7 rads/mCi

C. Bone

Assume that the 1% (slow component) of the administered activity which is retained is totally in the bone and is eliminated by radiological decay only. Assume a bone mass of 10 kg and g = 20 then, the dose is 0.041 rads/mCi.

3. Summary

The following tables summarize the absorbed doses (rads/mCi):

Organ or Tissue	With Normal Kidney Function	With Abnormal Kidney Function	When 1% of Initial Activity is Retained
Bladder	1.7	1.7	-
Kidney	0.91	7.5	-
Bone	-		0.041

Relation to Permissible Body Burden

No reference was found to show the permissible body burden of Yb-169.

Rationale for Administered Dose

The administered doses (0.5-2 mCi) were selected from the results of clinical investigations sponsored by the 3M Company. The doses selected give an acceptably low radiation dose, and yet provide reliable diagnostic information.

APPENDIX C

SUMMARY AND REFERENCES

SUMMARY

Cisternography

Clinical investigators have administered Ytterbium (Yb 169) DTPA intraspinally to 121 patients in 3M sponsored clinical trials.[1] Wagner[2] and Deland[3] have published their experience with 30 and 125 cisternography studies, respectively, at the Johns Hopkins Medical Institutions. Intraspinal doses of ytterbium-169 ranged from 0.3 to 2.0 mCi. Scintillation imaging of cerebrospinal fluid dynamics was commonly performed at 0-3, 4-6, 24 and 48 hours after administration of the radiopharmaceutical. Delayed studies have been successful 96 hours after administration of the agent.

No adverse responses have been reported following intraspinal administration of Ytterbium (Yb 169) DTPA to the 121 patients in 3M Clinical trials or the 125 patients reported by Wagner[2] and Deland[3]. No significant changes were found in the hematological parameters for 39 patients, blood chemistry of 30 patients or urine chemistry of 39 patients. No changes in vital signs, neurological function or subjective feelings have been related to the injection of Ytterbium (Yb 169) DTPA. No changes have occurred in cerebrospinal fluid contents of 14 patients or cerebrospinal pressure of 9 patients after an intraspinal injection.

After intraspinal administration of Ytterbium (Yb 169) DTPA to four healthy patients or seven patients with cerebral atrophy, maximum levels of ytterbium-169 in blood were observed two to six hours after injection.[1] Following this, the level of radioactivity in blood decreased parallel to that in the CSF spaces. Urinary excretion of ytterbium-169 was identical for both types of patients,

and illustrated biological excretion of a fast component with an 8 hour effective half-time and a slow component with a 26 hour effective half-time. The average urinary excretion of the agent approximated 70 percent in 24 hours, 90 percent in 48 hours and 97 percent in 96 hours.

Following interpretation of Ytterbium (Yb 169) DTPA cisternography studies, only 33 of 76 patients required additional tests before a final diagnosis was obtained.[1] Results of the cisternography studies showed an abnormal CSF flow pattern for all patients diagnosed as having neurological abnormalities. Initial findings in five patients in whom cisternography demonstrated no abnormality did not correspond with a later diagnosis of cerebral atrophy in three, probable pseudotumor in one and mild hydrocephalus in a fifth.

References

1. Data available from Nuclear Products, 3M Company.

2. Wagner HN, Hosain FD, Reba RC, et al.: A new radiopharmaceutical for cisternography: chelated ytterbium-169. Radiology 95:121, 1970.

3. Deland FH, James AE, Wagner HN, et al.: Cisternography with ^{169}Yb-DTPA. J Nucl Med 12:683, 1971.

4. In addition, data collected by the 3M Company and published in their circular (J-MYCl or J-MDYB) was provided to us. A more detailed report of work cited above has been provided to the United States Atomic Energy Commission and to Agreement State Regulatory Personnel.