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A Preliminary Evaluation of F^{18}-Labeled Tetrafluoroborate As A Scanning Agent For Intracranial Tumors[1]

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Radioisotopic localization of intracranial space-occupying lesions has become a standard diagnostic procedure in many neurosurgical centers, utilized routinely in patients with suspicion of tumor or other focal intracranial lesion (1). Coincidence detection of the annihilation radiation from positron-emission has distinct advantages in comparison with simple gamma-emitting isotopes for the recording of such lesions (2). Of those positron-emitting isotopes which have been evaluated in man, Arsenic-72 and -74 as sodium arsenate have been the isotopes of choice (3) from a localization standpoint. However, the long half-life of As^{74}, 17.5 days, and the fact that it is cyclotron-produced are major disadvantages. Copper-64 chelates have been used to circumvent these two drawbacks of As^{74} (4). With the development of camera-type imaging devices (5,6), new opportunities for high-speed external visualization of isotopic concentrations and dynamic processes are presented. Under such conditions isotopes with half-lives shorter than 12.8 hour Cu^{64} have distinct utility.

The work of Anbar *et al* in producing (7) and utilizing (8,9) Fluorine-18, as a scanning agent, is of great significance in this recent development. F^{18} is a pure positron-emitter with a 112 minute half-life. Large single doses may be administered for the rapid localization of lesions and repeated tests performed within short time intervals. The whole body dose to the patient receiving the suggested amount of 1 mc of F^{18} is 0.05 rads compared with 0.42 rads for the usual dose of 3.0 mc of Cu^{64} and 1.8 rads for the diagnostic dose of 1.3 mc of As^{74}.

The present work is a series of studies with animals and with human patients using potassium fluoroborate labeled with F^{18}. It corroborates the excellent work of Askenasy *et. al.* (10) in the localization of intracranial lesions using the BF_4^{18} anion. The physical advantages of F^{18} and the possibility of labelling organic compounds, by the second stage reaction described below, suggest the potential utility of such materials as tumor-localizing agents.

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METHODS

F^{18} was prepared at the Massachusetts Institute of Technology reactor by the irradiation of lithium carbonate in the following sequential reaction:

$$Li^6\ (n,\alpha)\ H^3;\ O^{16}\ (H^3, n)\ F^{18}$$

The standard procedure used in the preparation of KBF_4[18] consisted of the irradiation of 3.0 g of unenriched Li_2CO_3 at a flux of 2×10^{13} n/cm²/ sec for a period of 7.5 hours, until saturation was achieved. The total yield was 35 mc of F^{18}. The lithium carbonate was dissolved in 13.5 ml of 6N hydrochloric acid and in this mixture was dissolved 113 mg of stable KBF_4. The potassium fluoroborate was crystallized in an ice bath, filtered, washed with 2 ml of ice water and recrystallized two more times. The crystallization also removed tritium produced in the reaction. The total F^{18} activity at the time of biological studies was about 6 mc with a specific activity of 130 μc F^{18}/mg KBF_4. For its

TABLE I

RADIOISOTOPIC UPTAKE IN MICE PER UNIT WEIGHT OF TISSUE[1]

	Interval after intravenous injection	*15 minutes*		*30 minutes*		*60 minutes*	
	Compounds	BF_4^-	F^-	BF_4^-	F^-	BF_4^-	F^-
	Number of animals in group	17	6	12	4	12	4
A	*% per Kg normalized to 70 Kg*	2.3	1.7	1.7	4.6	1.4	2.4
B	*Ratio, Tumor: Brain*	10.0	7.5	8.5	6.8	11.0	5.4
	Ratio, Tissue: Blood						
	Blood	1	1	1	1	1	1
	Brain	.05	.1	.04	.1	.04	.2
	Tumor	.5	.8	.3	1.0	.5	.9
	Skull	.4	6.3	.3	8.6	.3	11.7
C	Muscle	.6	.6	.1	.9	.2	.4
	Scalp	.6	.6	.4	.6	.5	.7
	Thyroid	.4	.6	.3	.5	.5	.3
	Kidney	.6	—	—	—	—	—
	Liver	.3	—	—	—	—	—

[1]Values are averages for the animals in each group.

use in man the compound was dissolved in 10 ml of isotonic pyrogen-free saline at the physiological pH.

In preparing the fluoride ion, the acidified solution of Li_2CO_3 was passed through a cation exchange column[1] to remove not only lithium but also the sodium-24 arising from the activation of trace amounts of sodium present in analytical grade Li_2CO_3. In this manner 90-95% of F^{18} produced was recovered in the eluant.

Toxicity studies with fluoroborate ion were carried out in white Swiss albino mice and in rabbits. Tissue distribution of BF_4^{18} and F^{18} ions were examined utilizing C_3H mice bearing subcutaneously implanted tumors which were originally ependymomas. Tissue studies were also performed in cats.

A limited series of scans using the mechanical brain scanner previously described (1,2) was performed with KBF_4^{18} on 10 patients who were tumor suspects. The administered dose in each case was 1 to 3 millicuries. The scans were performed at short time intervals after the intravenous injection.

In a number of these patients blood samples were collected at intervals after injection to determine blood clearance as a function of time. In another patient a series of blood samples was taken and urine samples collected to determine the blood clearance and excretion curves.

RESULTS

1. Toxicity.

In the toxicity studies, mice received intravenously 300 mg/kg and rabbits 120 mg/kg of KBF_4 without any apparent acute toxic symptoms. The animals

[1]Dowex 50.

TABLE II

FLUOROBORATE CONCENTRATION PER UNIT WT. OF TISSUE IN CATS[1]

	Ratios to Blood	*Ratios to Brain*
Blood	1	27
Brain	.04	1
Skull	.2	6
Muscle	.3	7
Scalp	.6	16
Lung	.9	
Kidney	.8	
Heart	.7	
Skin	.7	
Liver	.3	
Intestines	.5	
Adrenals	.5	
Pancreas	.5	
Fat	.1	

[1]Values are averages for four animals sacrificed 30 minutes after injection.

were kept alive over a period of six weeks without sequelae. These tests were carried out with a solution neutralized to pH 7, for at a pH range of 1 to 3 large volumes of KBF_4 are extremely toxic. Doses of the order of 5-6 mg/kg of neutral KBF_4 were injected into terminal glioblastoma patients with no adverse effects.

The chemical amounts needed for routine patient scanning were less than 0.5 mg/kg and from the above data no problems of pharmacological toxicity were expected or observed in the patient study.

2. Mouse tissue studies.

The isotopic uptake in the organs of the mice bearing subcutaneously transplanted tumors is shown in Table I. Six groups of animals were used, three receiving labeled fluoroborate ion and three groups receiving F^{18-}. Sacrifice times were 15, 30 and 60 minutes after injection.

The tissue concentrations are presented in three different ways. Line A shows the average blood uptake for each group of animals as percent of total injected dose per kilogram of tissue normalized to total animal weight of 70 kg.[1] This normalization is the standard compromise used for comparative tissue studies between individuals and species. The mouse values are somewhat lower than the human data shown in Figure 2, but still sufficiently similar to show a probable common metabolic mode.

Line B gives the tumor to brain uptake ratio. For fluoroborate ion this ratio was approximately 10 throughout the time interval 15 to 60 minutes, and indicating that fluoroborate ion might be a useful scanning agent.

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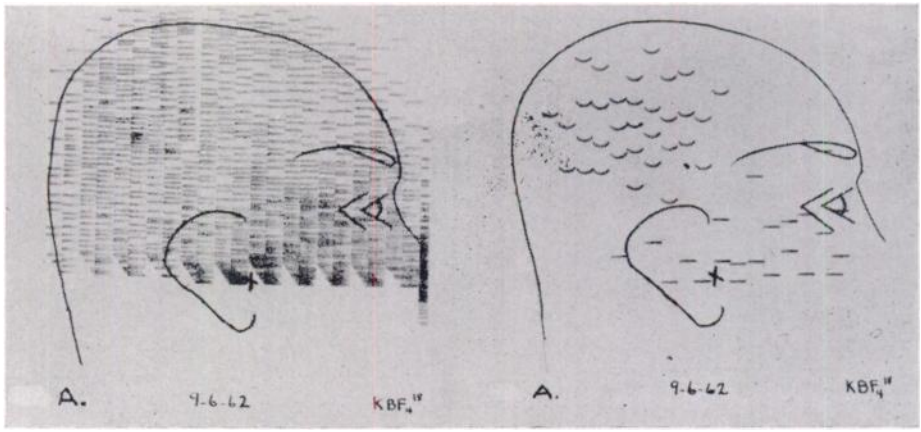
[1]Tissue Concentration (Normalized) = Concentration (Observed) $\times \frac{\text{Total wt in kg}}{70}$



1A
Coincidence Scan Showing Posterior-Parietal Concentration

1B
Unbalance Scan Curved Marks Indicate Right Concentration

Fig. 1. KBF_4^{18} Scan of Patient with Glioblastoma Multiforme

Section C presents the ratios of the uptake in other tissues to that in blood. These results are reasonably consistent averages since the standard deviation did not exceed 25 per cent. The greatest percentage uptake of the fluoroborate was in blood and the least in brain, while in other tissues and in tumor the distribution was nearly the same, with no organ having an exceptionally high level.

During this time interval fluoride ion showed a high concentration in blood compared to all other tissues studied except bone. The level in skull was about 6 times the blood level at 15 minutes and 12 times at 60 minutes. This high concentration of fluoride ion in bone militated against its use as a brain scanning agent, since the heavy concentration in the skull would mask any variations in the underlying brain.

A similar tabulation of the average values of the tissue uptakes of KBF_4^{18} in four cats sacrificed 30 minutes after injection is given in Table II. These values agree reasonably well with the mouse data in that the fluoroborate ion did not concentrate specifically in any particular organ.

3. Human patient studies.

A typical scan of one of the patients is shown in Figure 1. A clearly defined parietal concentration is indicated in the coincidence scan in 1 a. Figure 1 b, the unbalance scan, shows a concentration of curved marks indicating that the activity was on the right side. At operation a glioblastoma multiforme was found at the location indicated in the scan.

The data on the 10 patients scanned are summarized in Table III. The range of ages was from 6 to 72 years and included a series of neoplasms as well as one case of benign intracranial hypertension (pseudotumor). All of these

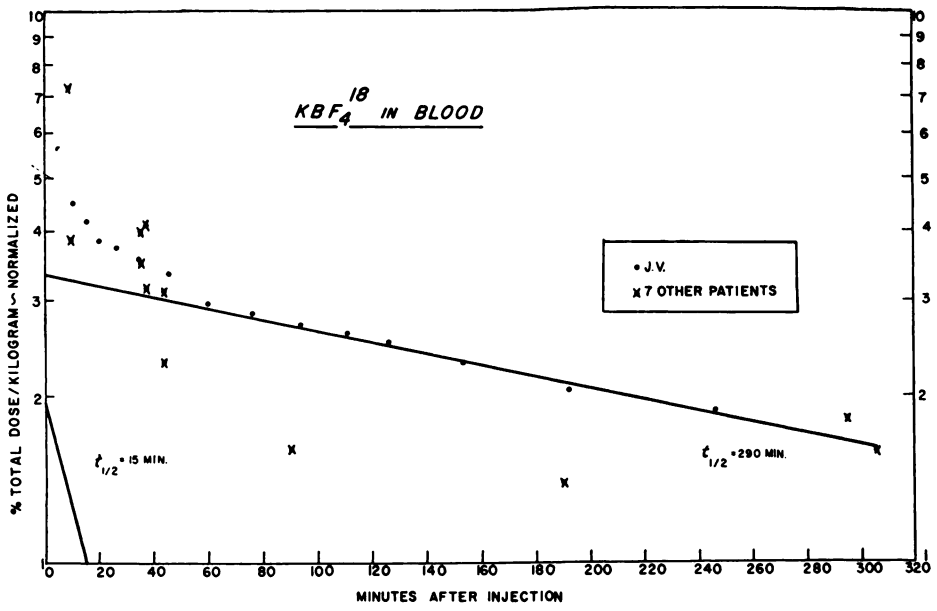


Fig. 2. Blood Clearance Study

patients were also scanned with arsenic or copper within a few days before or after the fluorine scan. The fluorine scan evaluations are indicated in the table with comments comparing the results obtained with the other tracers.

The blood clearance curve for the one patient (J.V.) from whom multiple samples were obtained, as well as 12 samples from 7 other patients, are plotted in Figure 2. There is a high degree of randomness in the data indicating that the absorption and excretion processes are highly individual. Using the data for J.V., the clearance curve seems to have two distinguishable time constants, a fast component with half time of about 15 minutes and a slow one with half time of 290 minutes. The rough agreement of the data of the other patients with J.V.'s curve indicates that this is reasonably normal.

Figure 3 is the cumulative urinary excretion curve for patient J.V. In the first few hours after injection the curve corresponds to an exponential excretion with half time of about 470 minutes. The rate becomes slower at longer times, but is difficult to evaluate numerically due to the short half life of F^{18}.

DISCUSSION

The animal tissue studies showed a high tumor:brain uptake ratio for fluoroborate ion, no unusually large concentration in any specific organ and no

TABLE III

PATIENTS SCANNED WITH F^{18}-TETRAFLUOROBORATE ANION

Patient	*Age*	*Diag.*	*Conf.*	F^{18}	As^{74}	Cu^{64}	*Comments*
A.	48	Glio. Mult.	Opn.	1	1	–	F^{18} similar to As^{74}
B.	38	Glio. Mult.	Opn.	2	–	1	Cu^{64} better than F^{18}
C.	6	Glio. Mult.	Opn.	1	1	–	F^{18} similar to As^{74}
D.	46	Astrcy. II	Opn.	4	–	4	Miss both isotopes
E.	57	Astrcy. II	Opn.	1	1	–	As^{74} pre-op; F^{18} post-op; question opn. artifact
F.	52	Pet. pyr. Mening.	Arter.	1	–	3	Question if we see bony involvement with F^{18}
G.	32	Meta. Melanoma	Auto.	3	–	1	Cu^{64} better than F^{18}
H.	42	Meta. Carcinoma	Opn.	2	2	2	All scans equally poor
I.	72	Chordoma	Radiol.	1	2	4	F^{18} better than As^{74} or Cu^{64}. Question uptake in bone-erosion
J.	12	Pseudo tumor	—	4	–	–	True negative

Notes

1—definitely abnormal
2—probably abnormal
3—probably normal
4—definitely normal

marked species variation. For these reasons it was considered suitable for evaluation in man.

The blood concentration curve is also favorable, since it is similar to that found in other useful scanning agents (3). Such curves characteristically display two or more time constants. The first should be very rapid, in the order of minutes, the second much longer of the order of hours. These time constants must be examined on the basis of several competing processes. The first time constant represents rapid initial removal from the blood and should be due to a general rapid interchange between blood and body tissue, rather than excretion or selective removal by a specific organ. The urinary excretion curve and the tissue studies indicate that for BF_4^- the last two processes are unlikely. The second time constant should represent the excretory removal of the agent from the blood. If a third, much longer time constant is observed, it represents the long term steady state interchange of the tracer between blood and body tissue, and the gradual excretion of the tracer.

With some isotopes, for example, ionic copper and ionic fluorine, the tracer is found in specific organs, liver and bone respectively, so that this general time sequence does not apply. However, the animal tissue studies of specific organs indicate that for KBF_4 there is no excessive preferential uptake.

Previous studies of blood clearance of arsenic indicate a similar curve with a fast component having a half-time of 46 minutes and a second component having a half-time of 27 hours (3). The more rapid initial component in the case

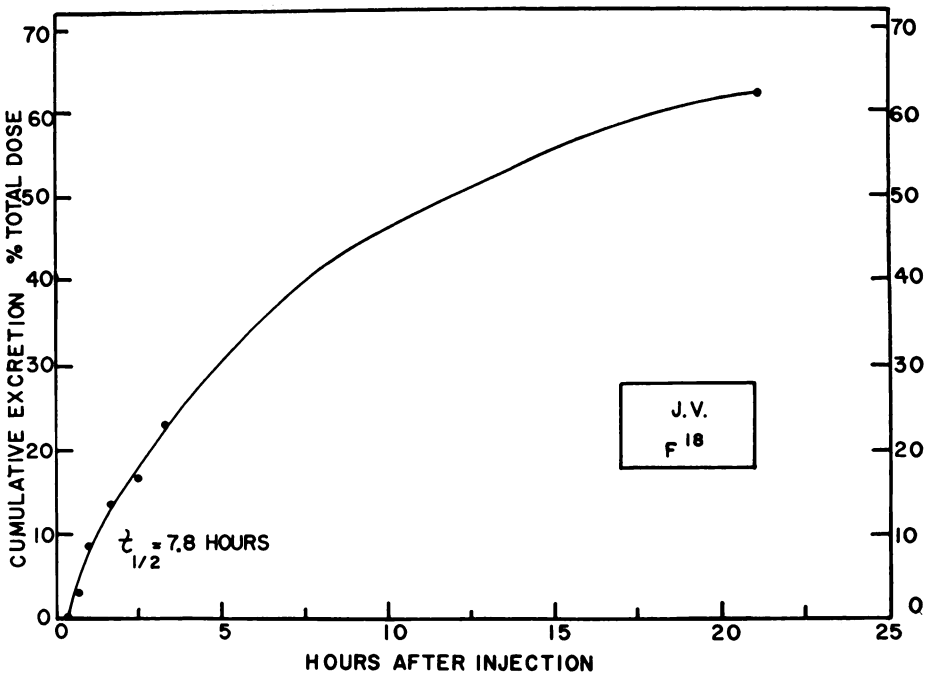


Fig. 3. Urinary Excretion Study of BF_4^{18} Anion

of the fluoroborate, 15 minutes, should assist in allowing scans to be made at much shorter intervals after injection. This hypothesis is borne out in the scans performed where a time lapse of about ½ hour seems to be optimal. This contrasts to 1½ hours with arsenic. The rapid initial fall-off should also be of assistance when the isotope is used for high-speed camera studies of dynamic processes.

While the number of scans performed, 10, is limited and therefore allows no generalizations, we do confirm the results obtained by Askenasy *et. al.* (1). In all cases except the benign intracranial hypertension in which there was no evidence of focal disease, the F^{18} scan was checked against a scan with arsenic or copper, or both.

The glioblastomas were clearly localized. In patient B, the fluorine scan was somewhat poorer than the copper, possibly due to the fact that the scan was begun 10 minutes after injection. This seems to be too short a time for good localization. In one case an astrocytoma was clearly missed with both isotopes and in another case was seen. This is consistent with the analysis of arsenic scans—that astrocytomas are frequently not seen. In patients F and I there was some bony involvement of the neoplasms. In both cases the visualization with fluoroborate was better than with other isotopes. There is a possibility, which is being investigated further, that some fluorine may be split off biologically from the complex ion and appear as fluoride ion going preferentially to such bone or that the BF_4^{18-} was contaminated with F^{18-} and a more rigorous purification of BF_4^{18-} is required. Patient G with metastatic melanoma was missed with fluorine though seen with copper, and patient H with metastatic carcinoma was visualized with all isotopes but equally poorly.

Summarizing these cases we think that labeled fluoroborate ion may prove to be a satisfactory scanning agent and should be explored further. These findings corroborate the work of Askenasy et. al. though their method of oral ingestion has not been used. It is suggested that for intravenous use the injection be performed one-half hour to one hour prior to scan at a dosage of 15 μc/kg, approximately 1 millicurie per 150 lbs. With this dosage, scanning may be performed on a mechanical scanner at a speed higher than usual, requiring approximately 25 minutes per scan.

Although this series of scans reveals no unusual physiological advantages of BF_4^{18} as a conventional scanning agent, its physical properties must be emphasized. Administration of 20 to 40 mc, giving a whole body dose of only 1 to 2 rads would be permissible for routine scanning and even higher doses would be appropriate for patients with known focal lesions. While these higher doses per se do not guarantee better diagnostic accuracy, they would allow greatly refined resolution with currently used scanning times. Alternatively the scanning time might be appreciably reduced. These improvements could open new avenues for scanning procedures such as transient studies.

SUMMARY

F^{18}, a 112 minute half-life positron-emitter was studied as a possible agent for brain tumor localization. Tissue studies in mice bearing subcutaneously transplanted tumors indicated that labeled potassium tetrafluoroborate showed

good preferential uptake in tumor compared to brain with no excessive concentration in other organs. F^{18} labeled sodium fluoride gave very high concentrations in bone and is not suitable as a brain scanning agent. Tissue studies in cats with the fluoroborate ion confirm that there is no appreciable preferential tissue uptake. Blood studies in humans showed a suitable fall-off of the level of activity using the fluoroborate ion and a preliminary study of a small number of patients scanned with fluoroborate and other isotopic agents indicate that the former appears to be a suitable compound for brain tumor localization and merits further study.

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BIBLIOGRAPHY

1. SWEET, W. H., MEALEY, J., ARONOW, S., AND BROWNELL, G. L.: Localization of Intracranial Lesions by Scanning with Rays from Positron-Emitting Isotopes. *Clinical Neurosurgery,* 7:159, 1957.
2. BROWNELL, G. L.: Theory of Isotope Scanning in *Medical Radioisotope Scanning* I.A.E.A., Vienna. p. 1-12, 1959.
3. MEALEY, J., BROWNELL, G. L., AND SWEET, W. H.: Radioarsenic in Plasma, Urine, Normal Tissues and Intracranial Tumors. *A.M.A. Arch. of Neurol. and Psych.* 81:310, 1959.
4. BAGNALL, J. H., BENDA, P., BROWNELL, G. L., AND SWEET, W. H.: Positron Scanning with Copper-64 in the Diagnosis of Intracranial Lesions. *J. of Neurosurg.* 15:411, 1958.
5. ANGER, H. O., AND GOTTSCHALF, A.: Localization of Brain Tumors with the Positron Scintillation Camera. *J. of Nuclear Med.,* 4:326, 1963.
6. ARONOW, S.: Electronic Developments in Positron Scanning. Proc. 2nd Int. Conf. on Med. Electron., Paris, 568-578, 1959, Iliffe & Sons, London.
7. ANBAR, M. AND NETA, P.: The Chemical Behavior of Fuorine-18 Produced by the $O^{16}(H^3n)$ Nuclear Reaction. *J. Am. Chem. Soc.* 84:2673, 1962.
8. ANBAR, M., ASKENASY, H. M., GUTTMANN, S., KOSAY, I. Z., LAOR, Y. AND LEWITUS, Z.: Brain Tumor Location. Semi-Annual Report—Israel Atomic Energy Commission. 75-78, July—December, 1960.
9. ANBAR, M. AND ERNST, N.: A Distribution Study of F^{18}—Labeled Cationic Flourocomplexes in Rats. *Int. J. Appl. Radiation and Isotopes.* 13:47, 1962.
10. ASKENASY, H. M., ANBAR, M., LAOR, Y., LEWITUS, Z., KOSAY, I. Z. AND GUTTMANN, S.: The Localization of Intracranial Space—Occupying Lesions by Fluoroborate Ions Labeled with F^{18}. *Amer. J. Roentgenol.* 88:350, 1962.