

UPTAKE OF ^{13}N -LABELED AMMONIA

W. G. Monahan, R. S. Tilbury, and J. S. Laughlin

Sloan-Kettering Institute for Cancer Research, New York, New York

Ammonia has a vital role in the metabolic activities of organs including the kidney, liver, and brain, in particular in the biochemical pathways leading to amino acids, purines, and urea. The objective of the work reported here is part of an overall research program to produce and study the metabolism of new cyclotron-produced radioactive compounds which will have useful applications in medical research and diagnosis (1). This is a report of findings, based on dog studies, which indicate that ^{13}N -labeled ammonia has several potential uses: (A) as a short-lived agent for tumor scanning; (B) as a measure of kidney function; and (C) for imaging myocardium and liver (2). These studies suggest that $^{13}\text{NH}_3$ will prove valuable in organ scanning and metabolic studies of patients.

MATERIALS AND METHODS

Ten-minute ^{13}N is the longest lived of the radioactive isotopes of nitrogen and the only practicable tracer for medical studies. Its 100% decay by positron emission coupled with its short physical half-life offers an optimum ratio of clinical information to modest radiation dose. We have been able to produce millicurie quantities of ^{13}N -labeled ammonia from the relatively simple reaction of deuterons on methane gas. The $^{13}\text{NH}_3$, dissolved in saline, is of high purity (>98%) and high radioactive concentration (up to 10 mCi/cc). The large photon flux has made possible dynamic studies in normal dogs and in dogs with malignant neoplasms for periods of more than 30 min with the Total Organ Kinetic Imaging Monitor (TOKIM) (3) and the High Energy Gamma (HEG) (4) scanner systems.

Nitrogen-13-labeled ammonia was first produced by Joliot and Curie in 1934 by irradiation of boron nitride with ^{210}Po alpha particles (5). It has been produced in usable quantities by irradiation of metallic carbides, particularly aluminum carbide, with 7-MeV deuterons, by means of the d,n reaction

on ^{12}C (6,7). On dissolving the aluminum carbide in either acid or alkali, ammonia labeled with ^{13}N is produced which is recovered by distillation (6). A disadvantage of this method is that ^{28}Al is also produced in the irradiation, which, with its 2.4-min half-life and high-energy beta and gamma radiation (1.78 MeV) constitutes a considerable radiation hazard in handling and processing the target.

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For reprints contact: John S. Laughlin, Div. of Biophysics, Sloan-Kettering Institute for Cancer Research, New York, N.Y. 10021.



FIG. 1. Whole-body scans of normal dog following intravenous injection of ^{13}N -labeled ammonium chloride.

In the method developed here for this work, continuously flowing methane gas is irradiated with 8-MeV deuterons in a Pyrex glass-lined target chamber. The gas is then bubbled through water or isotonic saline in which the ammonia dissolves. By irradiating at 5 μ A for 10 min and allowing the methane to flow at 1.5 liters/min for an additional 5 min, 20 mCi of $^{13}\text{NH}_3$ activity can be collected in a bubbler. A decay study of the radioactivity in the bubbler showed a pure 10.0-min half-life from 5 to 95 min after the end of irradiation. Analysis of the solution in the bubbler by radioactive gas chromatography showed that the radioactive products were 95% $^{13}\text{NH}_3$, 2% CH_3NH_2 , and 0.2% $\text{C}_2\text{H}_5\text{NH}_2$. Less than 3% HC^{13}N was detected in the solution and no $\text{CH}_3\text{C}^{13}\text{N}$ was detected. The HC^{13}N was removed by passing through a column of soda-lime. This method of producing ^{13}N -labeled ammonia is described in more detail elsewhere (8).

RESULTS AND DISCUSSION

Figure 1 shows computer printouts of two whole-body scans, ventral and lateral aspects, of a normal dog 5 min after intravenous injections of 13 mCi and 10 mCi of ^{13}N -labeled ammonium chloride, respectively. The scans were performed from head to tail using a 19-hole tungsten collimator, and the outputs were not corrected for physical decay. The scans show uptake in the brain, possibly the salivary glands, the heart, liver, and bladder. Uptake of ammonia in liver, brain, and kidney was expected (9,10). The kidneys are not visualized very well in this scan since the radioactive ammonia is taken up immediately in the kidney and washes out with a half-time of about 10 min.

The myocardium is clearly visualized in these scans. This was not a predictable result since there is no established mechanism for accumulation of

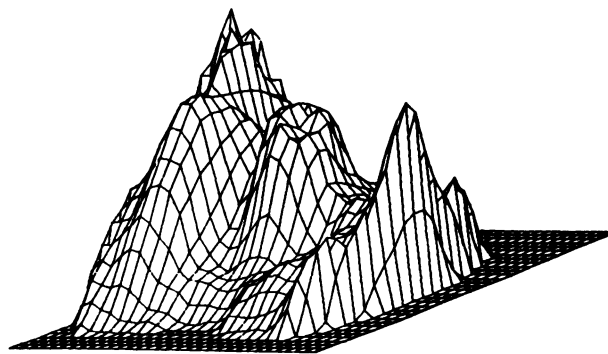


FIG. 2. Isometric output for TOKIM scan of normal dog performed 40 min after inhalation of approximately 5 mCi of $^{13}\text{NH}_3$ gas. From right to left, scan shows trachea, heart, and liver. Scan time was 10 min for 200,000 total counts.

ammonia in myocardium. Possible mechanisms include the fixation of $^{13}\text{NH}_3$ as a rapidly metabolized nitrogen such as the amine group of glutamine and the amine group of adenine nucleotides. Other possibilities include ionic exchange with bound NH_4^+ or other ions. In the metabolic studies initiated, routes of administration including inhalation, intravenous injection, and subcutaneous injection have been compared. All three methods of administration have yielded similar results with respect to myocardial imaging. Figure 2 shows an isometric display of a TOKIM scan of a normal dog performed 40 min after inhalation of approximately 5 mCi of carrier-free $^{13}\text{NH}_3$ gas. The initial inspiration was held for 1 min. The scan clearly shows activity in the trachea, heart, and liver. There is a slight depression in the center of the heart activity profile indicating the position of the ventricles. Some very good scan images were obtained by subcutaneous injection of high volume-specific activity $^{13}\text{NH}_4^+$. Figure 3 shows scintiphotos of TOKIM scans in the ventral and lateral aspects of a normal dog. These scans were performed 30–40 min after subcutaneous in-

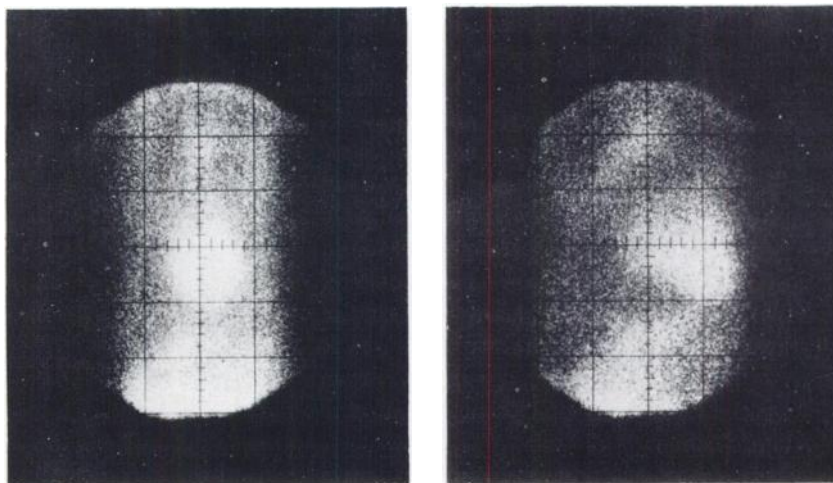


FIG. 3. Scintiphotos produced with TOKIM for ventral (left) and lateral (right) chest scans of normal dog following 9-mCi subcutaneous injection of ^{13}N -labeled ammonium chloride. Scans were performed between 30 and 45 min after injection and contain 300,000 and 200,000 counts, respectively.

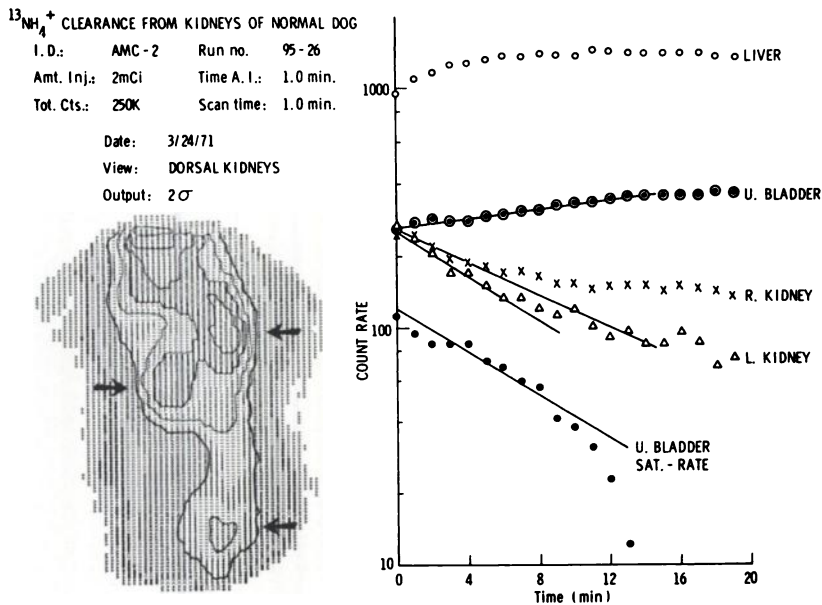


FIG. 4. Washout of ^{13}N -labeled ammonium chloride from kidneys of normal dog and accumulation in urinary bladder. Scan shows areas selected in dorsal aspect.

jection of 9 mCi in the neck. Levels of activity in heart and liver observed by all three methods were approximately the same.

Approximately 10–20% of the injected ammonium chloride activity is removed quickly from the blood stream by the kidneys and collected in the urinary bladder. The mean half-times for clearance from the kidneys of the three dogs studied are 10.6 and 7.7 min for the right and left kidneys, respectively. The right kidney is adjacent to the liver, which is accumulating ^{13}N and contributing to the counting rate for the selected area. Figure 4 shows a plot of the washout of ^{13}N from the kidneys and the accumulation in the urinary bladder and liver for a normal dog. The computer printout shows the areas selected for the dynamic study. Note that the rate of excretion of ^{13}N in the kidneys is the same as the rate of accumulation in the bladder. This is indicated by the slopes of the washout curves and the curve produced by subtracting the saturation value in the bladder area.

The application of $^{13}\text{NH}_4^+$ to the detection of neoplasms has also been explored. This work has been limited to scanning three dogs which had suspected spontaneous tumors. Of the three only one had a tumor, a thyroid carcinoma, which was confirmed at necropsy. Figure 5 shows a ventral view of the neck of this dog, obtained with the TOKIM, 10 min after an i.v. injection of ^{13}N -labeled ammonium chloride. The tumor mass is clearly indicated in this scan. There is no apparent uptake of ^{13}N above blood background in the area of the thyroid glands in scans of normal dogs.

SUMMARY AND CONCLUSIONS

A method has been developed for the production of ^{13}N -labeled ammonia in usable quantities with negligible contamination. Studies in dogs have characterized the uptake and clearance rates of the

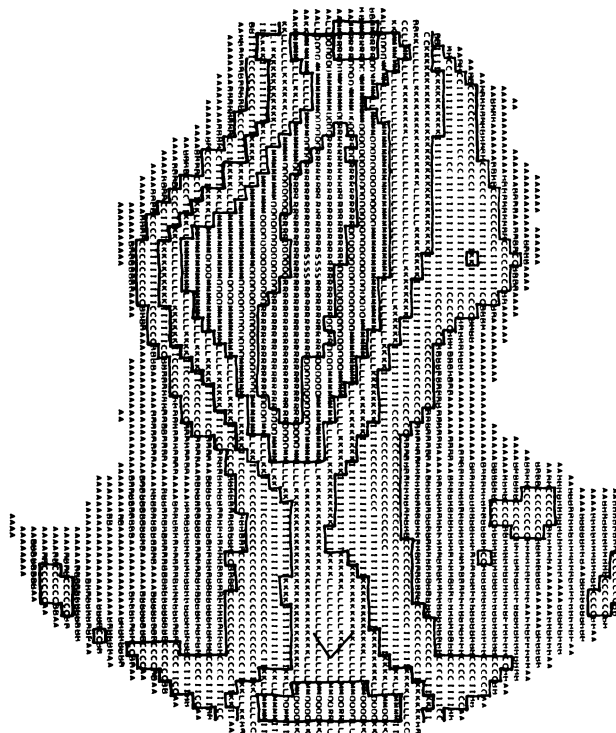


FIG. 5. Ventral scan of neck of dog with thyroid carcinoma 10 min after injection of ^{13}N -labeled ammonium chloride. Scan time was 9 min and the output contains 300,000 counts in 2-s.d. intervals. Supra sternal notch location is indicated, and nose is above top of field of view: region outlined with R symbols included coincided with tumor geometry.

labeled compound in myocardium, liver, and kidney. The early metabolic pathway of ammonia is not known but can now be more readily studied. This includes studies of the possibility of synthesis leading to the amide group of glutamine which can be incorporated into purine nucleotides and to carbamoyl phosphate and urea. This radioactive pharmaceutical appears to be a promising myocardial scanning agent with an excellent information to radiation dose ratio. It should also be useful for kidney and liver function studies and has potential as a soft-tissue tumor scanning agent.

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Dept. of Radiology
Peter Bent Brigham Hospital
721 Huntington, Ave.
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