Tissue Distribution Studies of [^{18}F]Haloperidol, [^{18}F]-β-(4-Fluorobenzoyl)propionic Acid, and [^{82}Br]Bromperidol by External Scintigraphy

G. A. DIGENIS *x, S. H. VINCENT *, C. S. KOOK *, R. E. REIMAN ‡, G. A. RUSS ‡, and R. S. TILBURY ‡

Received October 1, 1980, from the **Divisions of Medicinal Chemistry and Nuclear Medicine, Colleges of Pharmacy and Medicine, University of Kentucky, Lexington, KY 40506*, and the ‡*Sloan-Kettering Institute for Cancer Research, New York, NY 10021.* Accepted for publication February 12, 1981.

Abstract □ Tissue distribution studies of [^{18}F]haloperidol and [^{82}Br]-bromperidol, two potent neuroleptic drugs, were performed in rats by serial sacrifice. The usefulness of external scintigraphy in obtaining tissue distribution data in large animals is demonstrated by the tissue distribution of [^{18}F]haloperidol in rhesus monkeys. Both serial sacrifice and external scintigraphic studies demonstrated that uptake of the two drugs after intravenous administration into their target organ, the brain, was very fast and that the ratio of brain to blood levels was high throughout the 2-hr observation. Bromperidol appeared to reach peak brain levels faster than its chloro analog, haloperidol. Both bromperidol and haloperidol concentrated overwhelmingly in the rat lung. Haloperidol also showed a high affinity for the monkey lung. The disposition pattern in rats of [^{18}F]-β-(4-fluorobenzoyl)propionic acid, an apparent intermediate in butyrophenone metabolism, was entirely different from that of the parent drugs. This metabolite did not concentrate in the rat brain.

Keyphrases □ Haloperidol, radiolabeled—tissue distribution studied in rats and rhesus monkeys using external scintigraphy and serial sacrifice □ Bromperidol, radiolabeled—tissue distribution studied in rats and rhesus monkeys using external scintigraphy and serial sacrifice □ Radionuclides—radiolabeled bromperidol and haloperidol, tissue distribution studied in rats and rhesus monkeys using external scintigraphy and serial sacrifice □ Neuroleptic agents—haloperidol and bromperidol, tissue distribution studied in rats and rhesus monkeys using external scintigraphy and serial sacrifice

The increased availability of short-lived radionuclides and radiopharmaceuticals and the growing accessibility of γ-counting facilities have made external scintigraphy a valuable analytical and diagnostic tool in radiopharmacy and nuclear medicine. Being noninvasive, external scintigraphy is particularly useful for providing information on the disposition of drugs in humans as well as in large mammals where large colonies of isogenic subjects are unavailable. Conventionally, such information is obtained by extrapolation from experimental animal data and measurements of blood and urine levels in humans. Such an approach neglects any inter- or intraspecies difference and assumes that drug levels in the target organ is proportional to blood levels. Unfortunately, this assumption may not be correct with certain neuroleptics of pharmacological interest. Such a discrepancy requires careful consideration, particularly when the dose regimen of a drug has to be adjusted on an individual basis.

External scintigraphic studies using compounds labeled with short-lived radionuclides provide at least a partial answer to this problem since such studies can provide information about tissue levels in humans. Additionally, repeated studies can be done using the same subjects, thus eliminating individual differences. *In vivo* distribution studies with compounds labeled with long-lived radioisotopes such as tritium and carbon 14 suffer from many disadvantages, the main one being that they are often inapplicable to humans.

External scintigraphy is particularly useful for short-term distribution and kinetic studies with compounds that are not metabolized extensively. This is particularly important since one main drawback of external scintigraphy is that it measures total radioactivity levels.

The present study attempted to demonstrate the usefulness of external scintigraphy and short-lived radionuclides as analytical tools in short-term tissue distribution studies of pharmaceutical drugs. Three butyrophenone compounds were chosen: haloperidol (II), β-(4-fluorobenzoyl)propionic acid (V), and bromperidol (VII).

BACKGROUND

Butyrophenone neuroleptics are a class of compounds whose blood levels do not necessarily reflect levels in the target organ or therapeutic response. Janssen and Allewijn (1) reported that the neuroleptic activity of haloperidol and several other butyrophenones correlated well with the drug concentrations in the brain but suggested that blood levels need not be related to parameters of interest. Large individual differences also seem to exist in the serum levels attained after butyrophenone administration. Forsman and Ohman (2) examined the steady-state concentration of haloperidol in serum in relation to the daily dose and found up to 10-fold differences between individuals. Zingales (3) reported, in a study of 14 patients, that a patient who gave a poor response to haloperidol therapy always had the highest plasma levels. These and other findings suggest that a simple correlation might not exist between butyrophenone plasma and behavioral changes. Thus, tissue distribution studies should be conducted directly in humans to obtain a correlation between blood levels, brain levels, and central nervous system (CNS) activity.

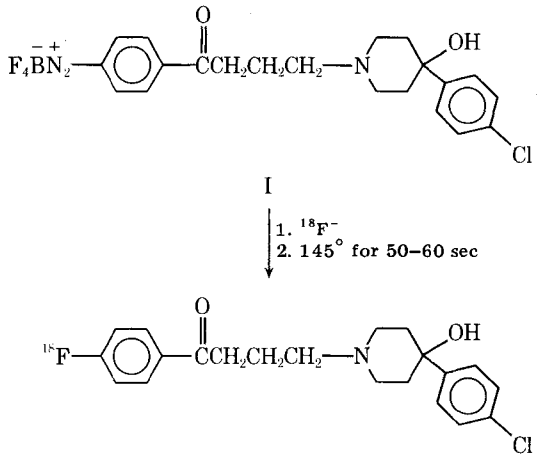
Haloperidol (II) is the prototype of the butyrophenone neuroleptics and is widely used in the treatment of hypomania, mania, and acute and chronic schizophrenia (4). Bromperidol (VII) is the bromo analog of haloperidol and currently is used in clinical trials. Preliminary reports on its pharmacology indicated that VII may have a faster onset and a longer duration of action (5, 6). Therefore, it seemed of interest to study the tissue distribution patterns of II and VII and to compare the times taken to reach peak levels in the brain, the target organ. The tissue distribution of V, one of their pharmacologically inactive metabolites (7), also was studied and compared to that of II and VII.

Metabolism studies (1) with tritiated butyrophenone neuroleptics have shown that 2 hr after subcutaneous administration, 80% of the radioactivity in the brain of rats is due to intact drug. Hence, during short-term studies, it is expected that metabolites do not contribute significantly to radioactivity levels in the various tissues, particularly the brain.

Neuroleptics II and V were labeled with fluorine 18, whereas VII was labeled with bromine 82.

Fluorine 18 is a pure positron emitter (0.635 Mev, β^+) with a physical half-life of 110 min. The resulting 511 kev annihilation radiation is detected easily by conventional nuclear medicine instrumentation such as external scintigraphy. Bromine 82 has a longer half-life (35.4 hr), and it decays with the emission of a β-particle (444 kev maximum energy) followed by several γ-rays. The principal photon is centered around 777 kev. These high-energy γ-emissions cause a "shine through" effect that results in distorted scintiphotographs when bromine 82 is used for external scintigraphic studies (8). This problem can be avoided by using bromine 77. Bromine 82 was used for these experiments because it is commercially

0022-3549/81/0900-0985$01.00/0



Scheme I—Principal reaction in the preparation of [^{18}F]haloperidol (^{18}F-II).

available. [^{77}Br]Bromperidol can be synthesized in the same manner as [^{82}Br]bromperidol.

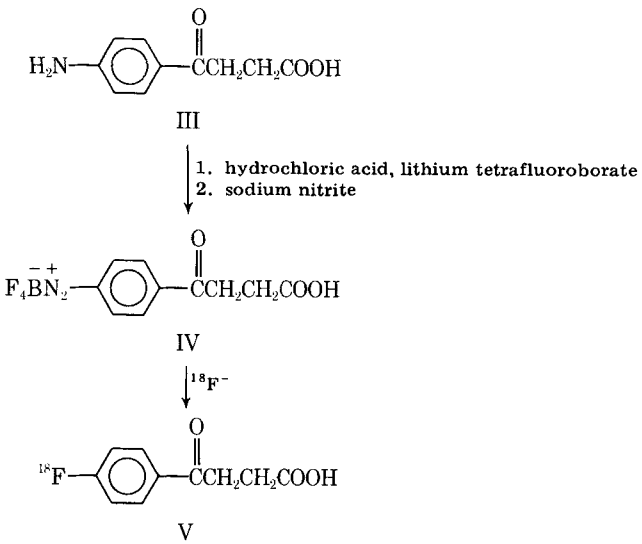
The synthesis of [^{18}F]haloperidol and [^{82}Br]bromperidol was reported elsewhere (9, 10). The synthesis of ^{18}F-labeled metabolite V and tissue distribution data of all three compounds in the rat and of [^{18}F]haloperidol in the rhesus monkey are reported here.

EXPERIMENTAL

Preparation of [^{18}F]Haloperidol (^{18}F-II)—Production of the radionuclide fluorine 18, used for the synthesis of ^{18}F-II, was accomplished by the irradiation of water with 22 Mev helium 3 particles produced by a cyclotron[1].

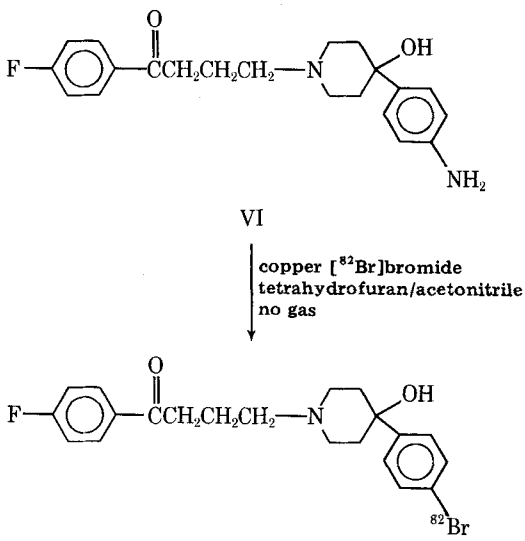
[^{18}F]Haloperidol was prepared from the diazonium tetrafluoroborate salt (I) (Scheme I) according to the previously published procedure (9). The specific activity of the purified product (column chromatography on neutral alumina) was 105 μCi/mg.

Synthesis of β-(4-Fluorobenzoyl)propionic Acid (V)—To 1.0 g (5.17 mmoles) of β-(4-aminobenzoyl)propionic acid (III) (11, 12) was added 9.0 ml of 18% HCl (Scheme II). The mixture was stirred vigorously and cooled to 5° in an ice bath. Then lithium tetrafluoroborate (1.59 g) in 3 ml of distilled water was added dropwise, followed by 3.0 ml of 10% $NaNO_2$. The solution was stirred vigorously for 15 min, and no precipitation was formed. The clear solution mixture was frozen in a dry ice–acetone bath and freeze dried for ~2 hr until most of the water was removed. The slurry was filtered through a sintered-glass funnel, cooled in dry ice, and washed with cold water. The brown solid (IV) was freeze dried again *in vacuo*.



Scheme II—Synthetic route for the preparation of [^{18}F]-β-(4-fluorobenzoyl)propionic acid (^{18}F-V).

[1] Model CS-15, Sloan-Kettering Institute, New York, N.Y.



Scheme III—Principal reaction in the preparation of [^{82}Br]bromperidol (^{82}Br-VII).

The dry tetrafluoroborate salt (IV) subsequently was pyrolyzed in xylene–dioxane (3:1) at 145° for 15 min, and the solvent mixture was evaporated on a rotary evaporator to dryness. The dark-brown pyrolysate was then dissolved in 5% aqueous sodium hydroxide. The solution was filtered through a sintered-glass funnel, and the filtrate was acidified with 5% HCl until it was acidic to litmus paper. The acidic solution was then extracted with three 15-ml portions of chloroform. The extracts were combined, dried with sodium sulfate, and evaporated to dryness on the rotary evaporator to yield 0.48 g (47.3% yield) of V, mp 100–105° [lit. (13) mp 102–103°]. The identity of V was proven unequivocally by mixed melting point (100–105°) and comparative spectroscopic determinations (IR and NMR) with authentic V[2].

Synthesis of [^{18}F]-β-(4-Fluorobenzoyl)propionic Acid (^{18}F-V)—Fluorine 18 was produced by the Van de Graaff generator through the $^{20}Ne(d,\alpha) \rightarrow {}^{18}F$ nuclear reaction, at the end of which the glass target insert was washed with 7.5 ml of distilled water. The volume of the water was reduced to ~1 ml by heating at 110° and by blowing nitrogen gas into the solution. To the aqueous solution containing 17.2 mCi of fluorine 18 were added 50 mg of the diazonium salt (IV) and 2.0 ml of acetone. After standing for 5 min, the solvents were removed on the rotary evaporator at 50°. The residue was dried further in the freeze drier for 30 min, and the dried salt subsequently was pyrolyzed in xylene–dioxane (3:1) as already described.

The dark pyrolysate was dissolved in 5% NaOH, the solution was filtered, and the filtrate was acidified with 5% HCl. The acidic solution then was extracted with three 5-ml portions of chloroform. The extracts were combined, dried with sodium sulfate, and evaporated to dryness. The residue was washed with ether to yield 24.5 mg (123.2 μCi) of ^{18}F-V. A radioscan of the thin-layer chromatogram of the product, developed in chloroform–cyclohexane–acetic acid (20:80:10) using a silica gel plate, showed that all activity was coincident with the spot of known V. The incorporation of fluorine 18 into the final product (V) was calculated to be 2.95%. The specific activity was 5.03 μCi/mg.

Preparation of [^{82}Br]Bromperidol (^{82}Br-VII)—[^{82}Br]Bromperidol was prepared from the aminoperidol VI according to the previously published procedure (10) (Scheme III). Copper(II) [^{82}Br]bromide was prepared *in situ* from potassium [^{82}Br]bromide obtained commercially[3]. The specific activity of the purified product (column chromatography on neutral alumina) was 440 μCi/mg.

***In Vivo* Distribution Studies**—*Animals*—Two mature healthy male rhesus monkeys and several male Sprague–Dawley rats, 300–500 g, were used. Monkeys A and B weighed 8.6 and 6.4 kg, respectively. The animals were allowed free access to food and water until the time of the experi-

[2] Aldrich Chemical Co., Milwaukee, Wis.

[3] New England Nuclear, Boston, Mass.

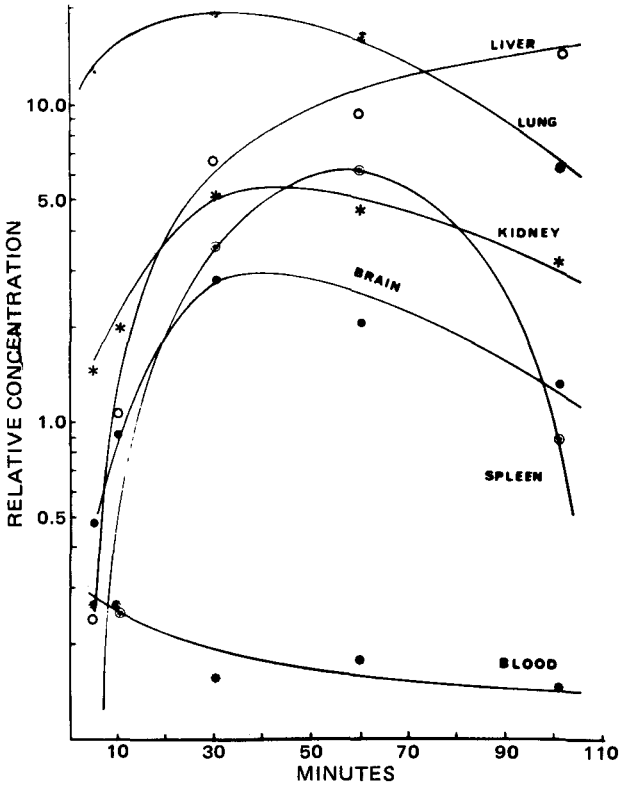


Figure 1—*Distribution of radioactivity following intravenous injection of [^{18}F]haloperidol (0.01 mg/kg, 0.8–0.9 μCi) in vital organs of the rat as a function of time. Each point represents average values from two rats. Relative concentration as defined by Woodard* et al. *(14) is: (counts of radioactivity in an organ/total radioactivity dose) × (weight of animal/weight of organ).*

ment. The monkeys were anesthetized with phencyclidine, and the rats were anesthetized with pentobarbital sodium solution.

Dose and Route of Administration—Solutions of [^{18}F]haloperidol (^{18}F-II), ^{18}F-V and [^{82}Br]bromperidol (^{82}Br-VII) were prepared immediately after their synthesis. Both ^{18}F-II and ^{82}Br-VII were dissolved in an appropriate volume of solvent mixture containing propylene glycol, ethanol, and water at pH 4, and ^{18}F-V was dissolved in the same solvent mixture at neutral pH. An aliquot of each solution was counted to determine the exact dose of radioactivity administered to the animals.

Monkey A was used for three rectilinear scans and received 0.52 mg of ^{18}F-II/kg (300 μCi) in the left femoral vein. Monkey B was used for

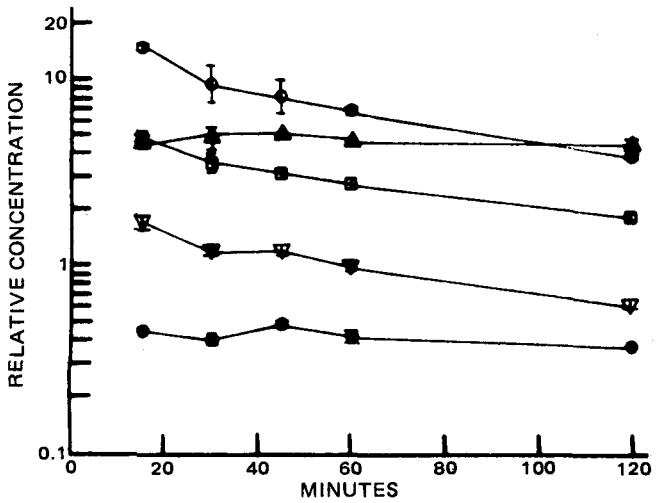


Figure 2—*Distribution of radioactivity following intravenous injection of [^{82}Br]bromperidol (0.2 mg/kg, 19–22 μCi) in various organs of the rat as a function of time. Each point represents average values in lungs (○), liver (▲), kidneys (□), brain (▽), and blood (●) from five rats.*

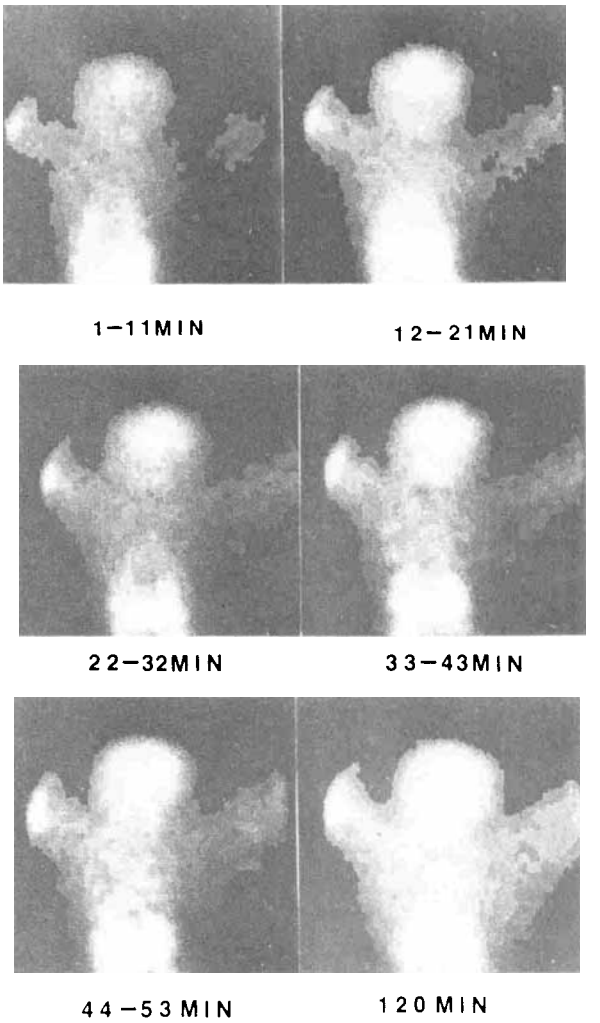


Figure 3—*Sequential computer-analyzed displays following intravenous injection of [^{18}F]haloperidol to a monkey, illustrating activity concentration in the brain and lung as a function of time.*

γ-camera scannings and received 1.05 mg of ^{18}F-II/kg (200 μCi). The rats received 0.01 mg of ^{18}F-II/kg (0.8–0.9 μCi), 0.01 mg of ^{18}F-V/kg (0.02–0.04 μCi), or 0.2 mg of ^{82}Br-VII/kg (19–22 μCi).

Tissue Distribution Studies—Following drug administration, the rats were sacrificed at various time intervals; a blood sample was withdrawn, followed by removal of the various organs. The samples were counted in a scintillation well-counter and corrected for decay. Radionuclide concentrations in the various organs were expressed by the relative retention method of Woodard *et al.* (14). Relative retention is defined as: (counts of radioactivity in an organ/total radioactivity dose) × (weight of animal/weight of organ). A high-energy γ-scanner was used for the rectilinear scans of Monkey A. The scans were performed 22, 82, and 142 min postinjection. Monkey B was used for the kinetic isotope distribution study with a γ-camera[4] (15).

RESULTS

The distribution of ^{18}F-II, ^{18}F-V, and ^{82}Br-VII in the vital organs of the rat as a function of time was determined by serial sacrifice of the animals. Figure 1 shows concentrations of fluorine 18 radioactivity (expressed as relative concentration) in various rat organs as a function of time after intravenous administration of ^{18}F-II. A similar plot for the bromine 82 concentrations obtained after intravenous administration of ^{82}Br-VII is shown in Fig. 2. The uptake of both II and VII into the target organ (brain) was very rapid. The bromine 82 concentration in the brain was already declining 15 min after administration, whereas the fluorine 18 concentration reached maximum levels 30 min after administration. Both II and VII were found to concentrate overwhelmingly in

[4] Total organ kinetic imaging monitor, TOKIM.

Table I—Tissue Distribution of [^{18}F]Haloperidol (^{18}F-II) at Various Time Intervals in Monkey A [a]

Organ	Percent Activity		
	22 min	82 min	142 min
Brain	2.3	2.7	2.2
Lungs	5.2	5.2	3.2
Liver	12.4	9.9	7.3
Kidneys	8.0	5.9	6.6

[a] Values represent percent activity in different areas (rectilinear scanning) over Monkey A. Loading dose was 0.52 mg/kg iv (300 μCi).

the lungs (Figs. 1 and 2, respectively), possibly due to their high lipophilicity. Their uptake by the liver also was very fast and continued throughout the observation period. Their blood levels, however, were relatively constant and much lower than the levels in the other organs. These data are in excellent agreement with those of Lewi *et al.* (16) who did experiments in rats with [^{3}H]haloperidol.

External imaging for the distribution of ^{18}F-II in the monkey was accomplished using the γ-camera (15). Figure 3 shows sequential computer-analyzed displays obtained after intravenous administration of ^{18}F-II. The results of the dynamic study are presented in Fig. 4. The uptake of II in the monkey lung was extremely rapid and reached a maximum level in the first 13 min. The initial uptake rate in the brain during this period also was fast. Between 10 and 20 min postinjection, the activity in the lungs did not change appreciably while that in the brain increased. After 20 min, the activity in the lung appeared to decrease (Fig. 4); a sharp decrease of activity was noted between 30 and 60 min. In contrast, however, the activity in the brain of the monkey did not change significantly over the same time interval. After 2 hr, the concentration of the drug and its metabolites was considerably decreased in the monkey lungs but remained at high levels in the brain (Fig. 3). In this connection, Janssen and Allewijn (1) showed that ~80% of the intact drug and 20% of its metabolites could be detected in the brain of the rat 2 hr after subcutaneous injection.

To obtain more information on the distribution of ^{18}F-II, three rectilinear scans were performed on Monkey A at 22, 82, and 142 min postinjection with the high-energy γ-scanner. Areas on the scan images corresponding to brain, lungs, liver, and kidneys were analyzed for activity

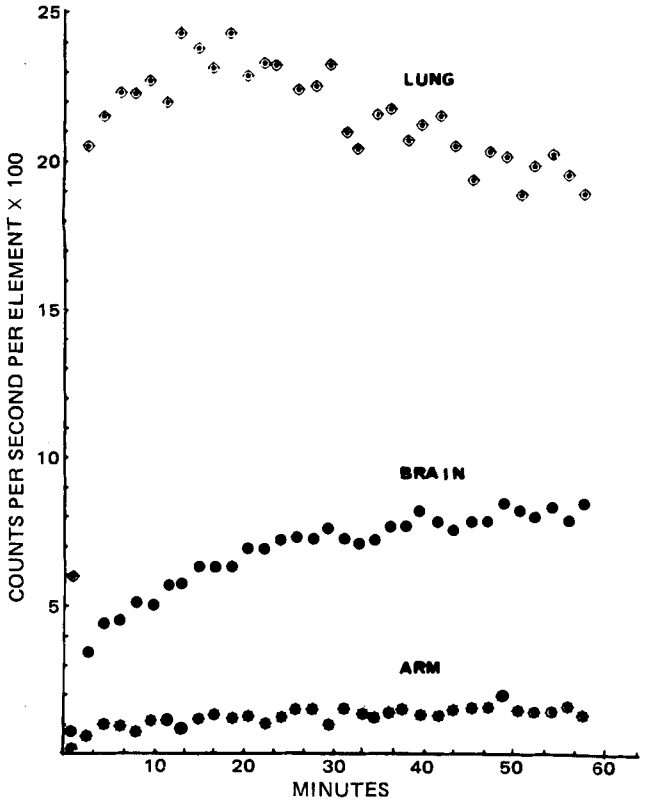


Figure 4—*Relative counts per second of [^{18}F]haloperidol (31.3 μCi/kg) in observed fields (head, lung, and arm) on Monkey B, obtained with the total organ kinetic imaging monitor technique (15).*

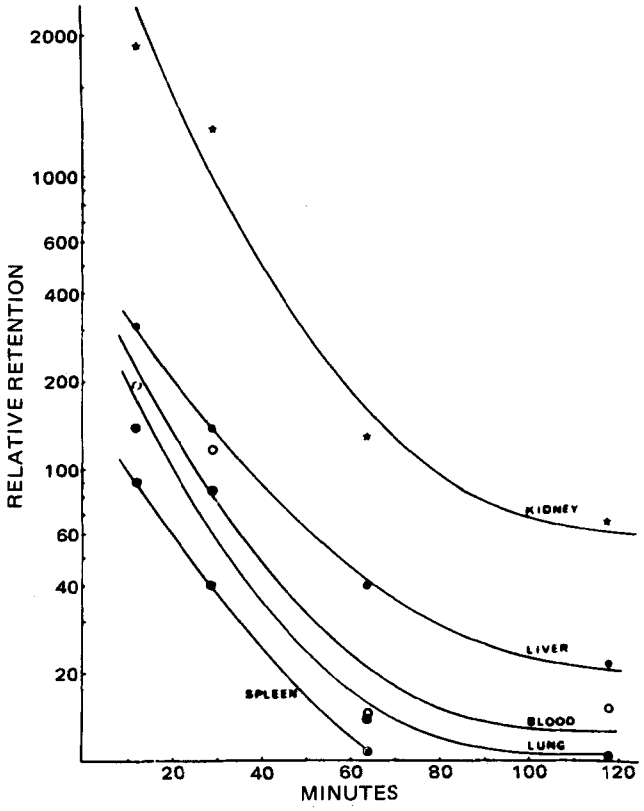


Figure 5—*Distribution of ^{18}F-V (0.01 mg/kg, total radioactivity dose 2–4 × 10^{-2} μCi) in vital organs of the rat as a function of time. Each point represents average values from two rats.*

content by computer techniques. The percentage of the injected dose in each area was obtained by dividing the total counts in the selected areas by the counts from the whole body of the monkey. From Table I, it can be seen that the brain uptake of II in Monkey A approached near maximum level in 22 min and remained fairly constant with time. These results are consistent with those obtained with Monkey B utilizing kinetic imaging (Fig. 4). The activity in the lungs and liver reached a maximum within 22 min. After 82 min, the activity in these sites started to decrease. Here again, the results obtained with the scanner on Monkey A paralleled those obtained by imaging on Monkey B. From the computer printouts, it was estimated that ~34.6% of the total radioactive dose could be detected in the bladder of Monkey A 82 min after injection; 44.6% was found after 142 min.

The metabolite of II (V), which was synthesized utilizing a Schiemann-type reaction (Scheme II), was injected into rats. The rats were sacrificed at different times as in the distribution study of II. Each organ was assayed in the scintillation well-counter, and the counts were corrected for decay. The relative concentration of radioactivity in vital organs was calculated according to the method of Woodard *et al.* (14). From Fig. 5, it can be seen that a sharp drop in plasma levels was observed over a 1-hr period following intravenous injection of ^{18}F-V, indicating a very fast distribution phase. The brain uptake was negligible, and the excretion rate from the kidney was very rapid. Elimination of V from the liver also was rapid.

DISCUSSION

An attempt was made to demonstrate the usefulness of short-lived radioisotopes coupled with serial sacrifice and/or external scintigraphy in obtaining short-term distribution pharmacokinetic data. The tissue distribution of two butyrophenone neuroleptics and one of their metabolites in rats and monkeys was compared. The main emphasis was on the levels of these compounds in the target organ, the brain. As already discussed, brain levels are the apparent parameter of interest in butyrophenone therapy; in humans, these levels can only be measured using external scintigraphy.

The uptake of haloperidol (II) and bromperidol (VII) by rat brain was faster than the uptake of II by monkey brain. However, the uptake was relatively fast in both animals, with the monkey brain showing an ap-

parent slow but continuous accumulation of fluorine 18 radioactivity. The pattern observed in the monkey was quite similar to that reported for barbiturates and antipyrine (17). Unlike these compounds, however, II and VII exhibited very high brain to blood levels. These results seem to correlate well with the fast onset and prolonged duration of neuroleptic effects of II and VII. It is assumed that during the initial portion of the observation period, radioactivity levels reflect concentrations of intact drug. Literature data (1) indicate that this assumption is valid.

Data obtained in the rat seem to indicate that VII may enter the brain at a faster rate than II. This finding apparently is in agreement with the pharmacological observation that VII has a faster onset of action than II (5, 6). However, the dose of ^{82}Br-VII administered to rats was much larger than that of ^{18}F-II. Hence, the observed difference in the profiles of the brain levels of the two drugs also could be attributed to dose-dependent kinetics. Lewi *et al.* (16) obtained data that indicate that early uptake of II into the brain may be proportional to the administered dose. Studies involving brain uptake and dose-dependent kinetics of ^{18}F-II and ^{82}Br-VII utilizing external scintigraphy are in progress.

Compound V is an important intermediate in the metabolism of butyrophenone neuroleptics (7). It is believed to be the first metabolite formed during the oxidative *N*-dealkylation of these compounds. Compound V had negligible brain uptake and was eliminated rapidly from the liver and kidney after intravenous administration to rats (Fig. 5). However, this and subsequent metabolites accounted for ~20% of the radioactivity found in the brain of rats 2 hr after subcutaneous administration of ^{3}H-II (1). Since V apparently is not partitioned into the brain, one may conclude from these findings that the metabolism of II and other butyrophenones may occur within the brain. If only the disappearance of radioactivity from the blood was followed, the relatively fast redistribution of V among the various tissues would be missed. External scintigraphy is a much more effective technique for following the tissue distribution of V since it allows continuous accumulation of data from the beginning of an experiment.

It is known that fluoride ions can replace the hydroxyl groups in hydroxyapatite crystals. Since the resulting fluoroapatite is more stable than hydroxyapatite, most fluoride ions administered to an animal concentrate in its skeleton. The present external scintigraphic studies with the monkey showed no accumulation of radioactivity in the area of the pelvis and knees. These anatomical areas were found to be regions of high free fluoride concentrations in rabbits (18). These data indicated that no ^{18}F-labeled free fluoride was produced *in vivo* as a result of ^{18}F-II administration. This finding strongly suggests that the carbon–fluorine 18 bond of the drug was not affected by its metabolism, a fact that is conversant with its high bond strength. Although the carbon–bromine bond is weaker than the carbon–fluorine bond, it is also believed that, during these experiments, there was no loss of bromine 82 from the aromatic ring of ^{82}Br-VII as the bromide ion. This assumption was substantiated by Sargent *et al.* (8) who found that only 5% of the radioactivity excreted in the urine over 24 hr was due to inorganic bromide following the administration of [4-^{82}Br]bromodimethylphenylisopropylamine to human subjects.

REFERENCES

(1) P. A. J. Janssen and F. T. Allewijn, *Arzneim.-Forsch.*, **19,** 199 (1969).

(2) A. Forsman and R. Ohman, *Nord. Psykiatr. Tidsskr.*, **28,** 441 (1974).

(3) I. A. Zingales, *J. Chromatogr.*, **54,** 15 (1971).

(4) C. J. E. Niemegeers and P. M. Laduron, *Proc. R. Soc. Med.*, **69,** Suppl. 1 (1976).

(5) C. J. E. Niemegeers and P. A. J. Janssen, *Arzneim.-Forsch.*, **24,** 45 (1974).

(6) W. Poldinger, E. Bures, and H. Haage, *Int. Pharmacopsychiatry*, **12,** 184 (1977).

(7) W. Soudijn, I. Van Wijngaarden, and F. Allewijn, *Eur. J. Pharmacol.*, **1,** 47 (1967).

(8) T. Sargent, D. A. Kalbhen, A. T. Shulgin, G. Braun, H. Stauffer, and N. Kusubov, *Neuropharmacology*, **14,** 165 (1975).

(9) C. S. Kook, M. F. Freed, and G. A. Digenis, *J. Med. Chem.*, **18,** 533 (1975).

(10) S. H. Vincent, M. B. Shambhu, and G. A. Digenis, *ibid.*, **23,** 75 (1980).

(11) J. P. Englis, R. C. Clapp, Q. P. Cole, and J. Krapcho, *J. Am. Chem. Soc.*, **67,** 2263 (1945).

(12) C. K. Chuang and Y. T. Huang, *Chem. Ber.*, **69B,** 1505 (1936).

(13) L. F. Fieser, E. Berliner, F. J. Bondhus, F. C. Chang, W. G. Dauben, M. G. Ettlinger, G. Fawaz, M. Fields, C. Heidelberger, H. Heymann, W. R. Vaughan, A. G. Wilson, E. Wilson, M. Wu, M. T. Leffler, K. E. Hamlin, E. J. Matson, E. E. Moore, M. B. Moore, and H. E. Zaugg, *J. Am. Chem. Soc.*, **70,** 3197 (1948).

(14) H. Q. Woodard, R. E. Bigler, and B. Freed, *J. Nucl. Med.*, **16,** 958 (1975).

(15) G. W. Monahan, W. J. Beattie, and J. S. Laughlin, *Phys. Med. Biol.*, **17,** 503 (1972).

(16) P. J. Lewi, J. J. P. Heykants, F. T. N. Allewijn, J. G. H. Dony, and P. A. J. Janssen, *Arzneim.-Forsch.*, **20,** 943 (1970).

(17) B. N. Ladu, H. G. Mandel, and E. L. Way, "Fundamentals of Drug Metabolism and Drug Disposition," Williams & Wilkins, Baltimore, Md., 1971, p. 83.

(18) A. Costeas, H. Q. Woodard, and J. S. Laughlin, *J. Nucl. Med.*, **11,** 43 (1970).

ACKNOWLEDGMENTS

Supported in part by National Institute of Mental Health Grant 5RO1 MH31577-02.

The encouragement of Dr. John S. Laughlin of the Biophysics Laboratory, Sloan-Kettering Cancer Institute, is gratefully acknowledged.