It is now apparent that there exist specialized transport mechanisms for riboflavin, other water-soluble vitamins, and certain amino acids and sugars for renal tubular reabsorption as well as intestinal absorption (3, 7, 23, 24). Both mechanisms are easily saturable. The specialized renal tubular reabsorption process helps to prevent a possible depletion of body levels of these essential nutrients. On the other hand, saturability of transport of nutrients across the small intestine sets an upper limit on the amount of these substances which can be absorbed.

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Distribution, Excretion, and Metabolism of ^{14}C-Labeled Quaternary Ammonium Salt of Mepazine and Promethazine in Rats

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Abstract □ Studies on the biological fate and antimicrobial activity of mepazine and promethazine methiodide are presented. Synthesis of ^{14}C-methiodide and estimation of the unchanged compound in biological materials are described. After intraperitoneal administration, the majority of these compounds was excreted in feces. The radioactivity in the liver and kidneys prevailed over other organs. Blood levels were low but above the significant level in both compounds. Brain level of promethazine methiodide-^{14}C was detectable but that of mepazine methiodide-^{14}C was insignificant. These compounds displayed a significant antimicrobial activity.

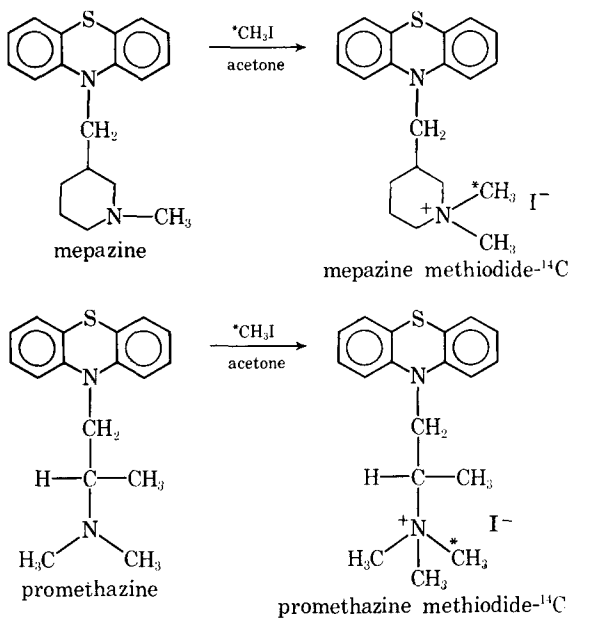
Keyphrases □ Mepazine and promethazine ^{14}C-methiodides—synthesis □ Biological fate—mepazine and promethazine ^{14}C-methiodides □ UV spectrophotometry—identity □ Paper chromatography—separation □ Radiochromatography—purity determination

Mepazine and promethazine are derivatives of phenothiazine but they display quite a different mode of action. Pharmacologically, mepazine is less potent than chlorpromazine (1–5). The drug possesses a neuroleptic effect similar to that of chlorpromazine (6–8); however, mepazine is not a drug of choice for the treatment of psychoses because of the high incidences of side effects such as agranulocytosis, seizures, depression of bone marrow, and jaundice. Promethazine (9, 10) finds its use mainly as a potent antihistaminic drug with a prolonged duration of action and as a drug for motion sickness. The difference in the pharmacological activities between these two drugs appears to be attributable to the effect of the side chains attached to the nitrogen of the phenothiazine ring system. All psychoactive phenothiazine derivatives possess a three-carbon bridge between the terminal and the ring nitrogen, while the presence of a two-carbon bridge between the two nitrogens appears to enhance the antihistaminic effect but diminishes the psychoactive properties of phenothiazine derivatives.

Quaternization of a side-chain nitrogen does not seem to decrease the toxicity of phenothiazine neuroleptics (11, 12). In many cases, toxicity appears to be enhanced.

A comparison was made on the distribution, excretion, and metabolism of ^{35}S-labeled promethazine and a quaternary phenothiazine compound (Aprobit) [1-(10-phenothiazinylmethyl)ethyl - 2 - hydroxyethyldimethylammonium chloride] on mice (13). Fecal excretion was found to be the major route of elimination of the quaternary phenothiazine compound after oral administration, but the drug was excreted mainly unchanged in urine after parenteral administration. Contrary to this report, the majority of the parenterally administered promethazine methiodide was found in the feces.

This study was undertaken to investigate the tissue distribution and excretion pattern in rats and antimicrobial activity of mepazine methiodide-^{14}C and promethazine methiodide-^{14}C. Brain level was low but above the significant level, which indicated a relatively low blood-brain barrier for these compounds. Biliary excretion was revealed to be the major route of elimination of these compounds. These data tend to confirm the belief that the affinity of molecules for the liver cell and consequently the metabolic mechanism of the liver are the decisive factors which determine the biological fate of a compound *in vivo*.



Scheme I—Synthesis of mepazine methiodide-^{14}C and promethazine methiodide-^{14}C

METHOD[1]

Synthesis of Mepazine Methiodide (MPZ-MEI) and Promethazine Methiodide (PMZ-MEI)—Mepazine hydrochloride (0.5 g.) was dissolved in water, and the solution was adjusted to pH 10 by adding sodium hydroxide solution. The oily precipitate which occurred was extracted several times with chloroform; the combined chloroform extracts were evaporated *in vacuo* to yield 0.46 g. of a viscous oil. The free mepazine base thus obtained was dissolved in 50 ml. of acetone, and 0.5 ml. of methyl iodide was added. The mixture was left standing for 15 min. Crystals, which appeared in the container, were collected and recrystallized from methanol to yield 0.56 g. (82%) of the product with m.p. 120–122°; $\lambda_{max.}$ 251 and 255 mμ.

Anal.—Calcd. for $C_{20}H_{25}IN_2S$: C, 53.09; H, 5.53; N, 6.19; I, 28.03; S, 7.08. Found: C, 53.21; H, 5.45; I, 27.92; N, 5.99; S, 7.06.

Similarly, promethazine hydrochloride (0.5 g.) was dissolved in water, adjusted to pH 10, and extracted several times with ether. The combined ether extracts were evaporated *in vacuo* to yield 0.45 g. of an oil. The free base of promethazine was dissolved in 20 ml. of acetone, and 0.3 ml. of methyl iodide in 5 ml. of acetone was added. The mixture was shaken occasionally for 20 min. Then ether was added to the mixture to precipitate the product. The crude product was recrystallized from methanol to yield 0.57 g. (85%) of the quaternary ammonium salt with m.p. 224–225°; $\lambda_{max.}$ 208 and 252 mμ.

Anal.—Calcd. for $C_{18}H_{23}IN_2S$: C, 50.70; H, 5.40; N, 6.57; S, 7.51. Found: C, 50.80; H, 5.51; N, 6.68; S, 7.58.

Synthesis of Mepazine Methiodide-^{14}C (MPZ-MEI-^{14}C) and Promethazine Methiodide-^{14}C (PMZ-MEI-^{14}C)—The synthesis of ^{14}C-labeled quaternary ammonium salt of mepazine and promethazine is shown in Scheme I. The free base of mepazine (0.1 g.) obtained as described was dissolved in 5 ml. of acetone, and ^{14}C-methyl iodide (0.25 mc., 8.5×10^{-3} mmole) in 10 ml. of acetone was added. After 15 min., 0.1 g. of unlabeled methyl iodide was added as a carrier. The mixture was shaken for 15 min. and cooled for 10 min. Crystals which appeared in the mixture were collected and recrystallized from methanol. The product, MPZ-MEI-^{14}C (0.11 g., 82%), had a melting point of 120–122° and specific activity of 0.46 μc./mg. Mixed melting point with an authentic specimen of mepazine methiodide did not show depression (120–122°).

In the same manner, 0.1 g. of the promethazine base obtained as described was dissolved in 5 ml. of acetone, and ^{14}C-methyl iodide (0.25 mc., 8.5×10^{-3} mmole) in 10 ml. of acetone was added. The mixture was shaken for 30 min. and 0.1 g. of unlabeled methyl iodide was added. Then ether was added to the mixture to precipitate the product. The precipitate was collected and recrystallized from ethanol to give 0.12 g. (86%) of the final product, PMZ-MEI-^{14}C, with a melting point of 224–225° and specific activity of 0.12 μc./mg. The physical properties of this compound were found to be identical with those of authentic promethazine methiodide.

The radiochemical purity of both MPZ-MEI-^{14}C and PMZ-MEI-^{14}C was checked by chromatography coupled with a radiochromatogram scanner, Actigraph III. The chromatograms of these compounds showed only one spot with matching R_f values (MPZ-MEI, 0.76; PMZ-MEI, 0.76) and color reactions (MPZ-MEI, pink; PMZ-MEI, purple with 50% sulfuric acid) with the respective parent compound; therefore, both methiodide derivatives were considered to be radiochemically pure.

Tissue-Distribution Studies—For the tissue-distribution studies, each of the preparations (3 mg. of MPZ-MEI-^{14}C and 10 mg. of PMZ-MEI-^{14}C) was suspended in sesame oil (1 ml.) and administered intraperitoneally to three rats weighing 250–300 g. The animals were sacrificed at various time intervals of 0.5, 1, 2, 4, and 8 hr. after injection. The liver, kidneys, spleen, heart, lungs, stomach, intestines, muscle, bone, blood, and brain were isolated, rinsed with normal saline solution and briefly dried, and the weights were recorded. A portion of each organ (1 g.) was weighed out, homogenized (except blood and bone) with 5 ml. of ethanol, and centrifuged. This process was repeated three times and the ethanol extracts were combined. An aliquot (2 ml.) was measured in a planchet and dried, and the activity was recorded. The activity remaining in the residue after the methanol extraction was also recorded. An aliquot of blood specimen was measured and dried directly in a planchet, and a portion of the bone (femur, dried at 250° for 2 hr. and ground to a powder) was placed in a planchet to record the activity. All activity recordings were carried out at a constant geometry and corrections were made for the self-absorption. Recoveries of 0.3–0.9 mcg. of added MPZ-MEI-^{14}C and PMZ-MEI-^{14}C from tissues were 91 ± 4 and 90 ± 5%, respectively.

Excretion Studies—For the excretion studies, a suspension of MPZ-MEI-^{14}C (10 mg./kg.) and PMZ-MEI-^{14}C (25 mg./kg.) in sesame oil was administered intraperitoneally to six rats weighing 280–310 g. The animals were maintained in metabolic cages and were given food and water *ad libitum*. Urine and feces specimens were collected every 12 hr. for the MPZ-MEI-^{14}C group and every 8

[1] Melting points were taken on a Fisher-Johns apparatus and were corrected. UV absorption spectra were recorded in a Perkin-Elmer model 202 spectrophotometer. Paper chromatograms were developed by an ascending technique in a solvent system, *n*-butanol–ethanol–water (5:2:2). Radiochromatograms were scanned in a radiochromatogram scanner, Actigraph III (Nuclear-Chicago). Albino rats were obtained from Southern Animal Farms, Prattville, Ala. Radioactivity in the tissues was recorded in a G-M counter (Tracerlab, model TGC-2).

Table I—Radioactivity[a] Recovered from Urine and Feces of Rats after Intraperitoneal Administration of Mepazine Methiodide-^{14}C

Time, hr.	Urine, %	Feces, %
12	9.60 ± 1.60	No specimen
24	6.00 ± 0.60	18.20 ± 1.50
36	3.75 ± 0.05	15.90 ± 0.50
48	1.60 ± 0.10	16.65 ± 1.25
60	0.95 ± 0.25	6.25 ± 0.05
72	0.83 ± 0.25	0.50 ± 0.20
84	1.15 ± 1.05	2.20 ± 2.00
96	0.15 ± 0.05	0.20 ± 0.01

[a] Mean percent of the administered activity ± standard error.

hr. for the PMZ-MEI-^{14}C group of animals. An aliquot (1 ml.) of urine specimens was measured in a planchet and dried, and the activity was recorded in a G-M counter. Feces were powdered and dried. A fraction (1 g.) of the specimen was weighed out and extracted three times with 2-ml. portions of methanol. The combined methanol extracts were evaporated to dryness and the activity of the residue measured.

Metabolic Studies—Two groups of rats (five rats in each group) were administered intraperitoneally with 1 g. each of MPZ-MEI-^{14}C and PMZ-MEI-^{14}C, respectively. Pooled urine (20 ml.) from each group of animals was condensed to about 2 ml. An aliquot of 0.5 ml. was placed on Whatman 3 MM paper, and the chromatogram was developed by ascending technique (14) in the solvent system previously mentioned. The chromatogram was scanned in a radiochromatogram scanner, Actigraph III (Nuclear-Chicago), and then sprayed with 50% sulfuric acid to detect nonradioactive metabolites.

Feces collected over a 5-day period from both groups of animals were powdered and extracted successively with ether and methanol in a continuous extraction apparatus. Fatty substances in ether extracts that did not have radioactivity or color reaction with 50% sulfuric acid were discarded. The methanol extracts were combined and reduced to about 1 ml. *in vacuo*. An aliquot of 0.5 ml. was chromatographed and treated as described for the urine specimens.

RESULTS

During the 5-day period, the MPZ-MEI-^{14}C group of rats excreted a total of about 82% of the administered radioactivity with 24% in the urine and 58% in the feces (Table I). In the PMZ-MEI-^{14}C group of rats, fecal excretion accounted for about 59% and urinary excretion represented 12% of the administered activity (Table II). In all cases, nearly 70% of the recovered activity in the urine was excreted in the first 24-hr. period. Feces specimens could not be obtained until after the first 24 hr. from the mepazine group and after 40 hr. for the promethazine group of rats. The recordings of the radiochromatogram scanner indicated only one peak on the chromatograms of the urine specimen from both MPZ-MEI-^{14}C and PMZ-MEI-^{14}C groups of animals; however, 50% sulfuric acid spray revealed two spots (R_f 0.76 and 0.65) on the chromatogram of MPZ-MEI-^{14}C urine. The spot with R_f 0.76, which appeared to be the major metabolite, was identified to be the unchanged MPZ-MEI-^{14}C. The second spot with R_f 0.65, which represented only a small portion of the urinary metabolites, was tentatively identified to be the *N*-demethylated mepazine. The chromatogram of the PMZ-MEI-^{14}C urine exhibited only one spot (R_f 0.76) after 50% sulfuric acid spray. This spot corresponded to the recorded peak on the radiochromatogram scanner. In contrast to the finding of Hansson and Schmitterlöw (13) on the hydroxyethyl chloride salt of promethazine in mice, fecal excretion was the major route of elimination of both quaternary ammonium salts of mepazine and promethazine in the rats. This difference in the route of excretion appears to be due to the different types of quaternary onium derivative and species of animals used in these studies. This type of excretion was similar to that recorded with trifluoperazine methiodide-^{14}C (15).

Table II—Radioactivity[a] Recovered from Urine and Feces of Rats after Intraperitoneal Administration of Promethazine Methiodide-^{14}C

Time, hr.	Urine, %	Feces, %
8	6.42 ± 1.90	—[b]
16	1.66 ± 0.09	—
24	0.97 ± 0.37	—
32	0.71 ± 0.01	
40	0.48 ± 0.04	36.14 ± 1.98
48	0.49 ± 0.12	12.52 ± 3.18
56	0.51 ± 0.01	6.78 ± 0.79
64	0.32 ± 0.10	1.47 ± 0.54
72	0.41 ± 0.04	1.21 ± 0.89
80	0.23 ± 0.01	0.83 ± 0.16

[a] Mean percent of the administered activity ± standard error. [b] No specimen was obtained.

Table III—Distribution of Radioactivity[a] in Tissues of the Rat after Intraperitoneal Administration of Mepazine Methiodide-^{14}C

Organs	Time, hr. 0.5	1	2	4	8
Blood	0.15[b]	0.60	0.92	0.24	0.10
Bone (femur)	0.41	0.53	0.64	1.23	2.00
Brain	—[c]	—	—	—	—
Heart	0.04	0.04	0.15	0.41	0.02
Intestines including contents	4.82	10.13	14.01	7.20	7.92
Kidneys	7.20	8.03	1.21	1.02	0.28
Liver	12.83	10.74	6.50	6.83	7.04
Lungs	0.12	0.36	0.32	0.46	0.08
Muscle	5.25	4.16	2.05	1.17	0.66
Stomach including contents	0.24	0.21	0.28	0.30	0.28
Urine[d]	—[e]	—	—	3.60	4.53
Abdominal washings	8.25	2.23	0.70	0.38	0.24

[a] Including activities of free and bound materials. [b] Percent of the administered activity. [c] Insignificant radioactivity. [d] Collected from bladder. [e] No specimen obtained.

For the activity recording, organs were homogenized and extracted with methanol. Approximately 90% of the activity was extracted in methanol; however, about 10% of the activity appeared to be bound to the protein and was not extracted in methanol.

In the MPZ-MEI-^{14}C group, the radioactivity in the liver and kidneys was found to prevail over other organs 0.5 hr. after the administration (Table III). Biliary excretion took place rapidly, which was reflected by a sharp rise in the intestinal level after 1 hr.

Table IV—Distribution of Radioactivity[a] in Tissues of the Rat after Intraperitoneal Administration of Promethazine Methiodide-^{14}C

Organs	Time, hr. 0.5	1	2	4	8
Blood	0.47[b]	0.68	0.45	0.05	<0.01
Bone (femur)	3.43	1.61	0.27	1.17	0.39
Brain		0.01	0.02	0.03	0.02
Heart	0.07	0.03	0.03	0.02	0.02
Intestines including contents	4.68	8.91	18.06	10.76	5.44
Kidneys	5.65	3.92	1.74	0.74	0.08
Liver	20.19	5.75	9.33	1.80	0.14
Lungs	0.10	0.14	0.09	0.10	0.03
Muscle	2.52	0.68	0.06	0.45	0.34
Spleen	0.46	0.19	1.05	0.03	0.01
Stomach including contents	0.26	0.28	0.61	0.02	0.08
Urine[c]	—[d]	—	—	5.19	54.30
Abdominal washings	7.76	1.19	0.67	0.41	0.25

[a] Including activities of free and bound materials. [b] Percent of the administered activity. [c] Collected from bladder. [d] No specimen obtained.

In the case of PMZ-MEI-^{14}C, the activity in the kidneys was the highest after 1 hr. (Table IV). Then the activity in the intestines of both MPZ-MEI-^{14}C and PMZ-MEI-^{14}C groups reached its peak at 2 and 4 hr. The rapid rate of absorption of these compounds from the injected site was indicated by a rapid decrease of the activity recovered in the abdominal washings.

Blood levels were low but above the detectable level in both groups of animals (Tables III and IV). The brain level of PMZ-MEI-^{14}C became detectable 1 hr. after the administration, but that of MPZ-MEI-^{14}C was below the significant level throughout the entire period of the experiment. MPZ-MEI-^{14}C appeared to have a particular affinity for the bone; activity in the bone started to increase at 0.5 hr. after the administration and reached its peak after 8 hr. (Table III). Since the bone represents an average of 45% of the total body weight of rats, the total activity accumulated in the bone was higher than in most organs except the intestines and liver at 8 hr. A similar finding was recorded with PMZ-MEI-^{14}C, except that the peak level in the bone was reached at 0.5 hr. In the MPZ-MEI-^{14}C group, the liver and muscle levels showed a peak at 0.5 hr. and declined rapidly thereafter. Other organs followed a similar pattern, except bone in which the activity continued to accumulate until a peak level was reached at 8 hr. (Table III).

The LD_{50} of MPZ-MEI-^{14}C and of PMZ-MEI-^{14}C on mice was 75 mg./kg. and 95 mg./kg., respectively, which are higher than that of the corresponding parent compounds, mepazine (115 mg./kg.) and promethazine (130 mg./kg.). These compounds displayed a comparable antimicrobial activity to that of trifluoperazine methiodide on *Escherichia coli* and *Staphylococcus aureus* at a concentration of 1 mcg./ml.

CONCLUSION

The intraperitoneally administered quaternary ammonium salts of both mepazine and promethazine were well absorbed by the rats. The majority of the drugs was accumulated in the liver and excreted in the intestines (Tables III and IV). Peak blood level was observed at 2 hr. for MPZ-MEI-^{14}C and at 1 hr. for PMZ-MEI-^{14}C. Both compounds showed the highest activity in the intestines 2 hr. after the administration. MPZ-MEI-^{14}C seemed to have a particular affinity for bones; the activity in the bone of rats started to accumulate at 0.5 hr. and reached its peak level at 8 hr. The total activity in the bone was higher than in most organs except the liver and intestines. The brain level of PMZ-MEI-^{14}C was above the detectable level at 1 hr.

Urinary excretion of the two compounds was fairly rapid; nearly 70% of the recorded activity in urine was excreted in the first 24-hr. period. Fecal excretion was the major route of the metabolism of these compounds; 58% of the activity of MPZ-MEI-^{14}C and 59% of PMZ-MEI-^{14}C were recovered during the 5-day period. The discrepancy between the results obtained in this study and those of Hansson and Schmitterlöw (13) is evidently due to the different quaternary onium derivatives and species of animals used in these studies.

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