Urinary Excretion of Meperidine and Its Metabolites

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Abstract □ The urine of male and female mice, rats, guinea pigs, rabbits, cats, and dogs, given meperidine hydrochloride, 20–40 mg/kg ip, was analyzed by GLC for meperidine, normeperidine, *p*-hydroxymeperidine, and total (free and conjugated) meperidinic and normeperidinic acids. More than 90% of the excreted drugs was found in the 24-hr urine. Meperidine was observed in the urine of mice, rats, guinea pigs, and cats, but only a trace amount was observed in the urine of rabbits and dogs. Normeperidine, *p*-hydroxymeperidine (except in the mice), and total meperidinic and normeperidinic acids were observed in all species. All of the species studied have the capacity to *N*-demethylate meperidine to normeperidine and to hydrolyze meperidine and normeperidine to their respective acids. The male has a higher *N*-demethylating activity than the female with the exception of mice. Ester hydrolysis is a major metabolic pathway for meperidine metabolism.

Keyphrases □ Meperidine—metabolism, urinary excretion in mice, rats, guinea pigs, rabbits, cats, and dogs □ Metabolites—of meperidine, urinary excretion in mice, rats, guinea pigs, rabbits, cats, and dogs □ Metabolism—of meperidine in mice, rats, guinea pigs, rabbits, cats, and dogs □ Excretion, urinary—meperidine and its metabolites in mice, rats, guinea pigs, rabbits, cats, and dogs □ Analgesics—meperidine and its metabolites, urinary excretion in mice, rats, guinea pigs, rabbits, cats, and dogs

Urinary disposition of meperidine and its metabolite, normeperidine, has been determined in humans (1–9) and monkeys (10), but little information is available for other laboratory species. In two rats, 50% of the injected *N*-^{14}C-labeled meperidine could be accounted for in the urine as radioactive material within 24 hr after subcutaneous administration (11). After administration of meperidine (125 mg/kg sc or 25 mg/kg iv) to rats, 3.7% of the dose was accounted for in the 24-hr urine as meperidine, 17% as normeperidine, and 11% as meperidinic acid (11). The major metabolites of meperidine are normeperidine and free and conjugated meperidinic and normeperidinic acids. Small amounts of other metabolites have been identified, including meperidine *N*-oxide (12), *p*-hydroxymeperidine (13), *N*-hydroxynormeperidine (14), and *p*-hydroxynormeperidine[1]. The known metabolic pathways of meperidine are shown in Scheme I.

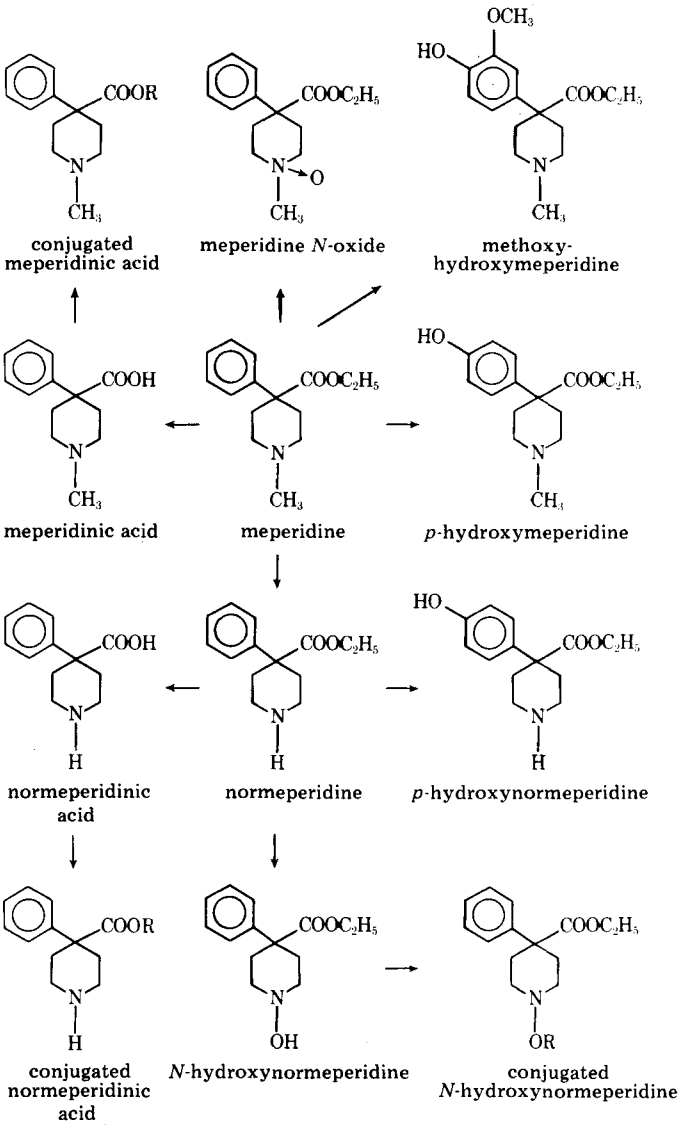
The analgesic effect of meperidine appears to differ among species, a phenomenon that may be due to differences in meperidine metabolism. Meperidine induces analgesia in mice (15–18), rats (19, 20), guinea pigs (21), cats (22), and humans (23) but not in dogs (24, 25). The present study was undertaken to investigate the differences in meperidine metabolism among species.

EXPERIMENTAL

Chemicals—Meperidine hydrochloride[2], normeperidine hydrochloride[2], *p*-hydroxymeperidine[3], and lidocaine hydrochloride[4] were used as received. Meperidinic and normeperidinic acids were obtained by alkaline hydrolysis of their respective esters. Other chemicals and solvents were analytical grade.

Animals—Animals were housed in air-conditioned quarters (23°) with 12-hr light and dark cycles. Food and water were given *ad libitum*. A dose of meperidine hydrochloride dissolved in 0.9% NaCl was administered intraperitonally to 28 male and 21 female Swiss Webster [Lai: Cox (Wi)] mice[5], five male and five female Wistar [Lai: Cox (XW)] rats[5], five male and four female Hartley albino guinea pigs[6], two male and two female New Zealand rabbits[6], two male and two female cats, and one male and one female beagle dogs. These animals were chosen because they are commonly used in biological research.

After drug administration, all animals except the mice were caged individually in stainless steel metabolic cages. The mice were housed in groups of seven to 10 animals per cage. The mice, rats, guinea pigs, and



Scheme I—Metabolic pathways of meperidine.

[1] S. Y. Yeh, unpublished data.
[2] Sterling-Winthrop Co., Rensselaer, N.Y.
[3] Obtained from Professor C. Lindberg, Biomedical Center, University of Uppsala, Uppsala, Sweden.
[4] Astra Pharmaceutical Products, Worcester, Mass.
[5] Laboratory Supplies, Indianapolis, Ind.
[6] Williams Farm, Fern Creek, Ky.

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Table I—Meperidine and Its Metabolites Found in Urine after Intraperitoneal Administration of Meperidine

Species and Sex (n)	Meperidine Hydrochloride, mg/kg	Collection Period, hr	Urinary pH	Mean[a], Equivalent Administered Dose, %					Total Drug Excreted	
				Meperidine	Normeperidine	p-Hydroxymeperidine	Total Meperidinic Acid	Total Normeperidinic Acid	24 hr	48 hr
Mice										
Male (3)[b]	40	0–24	7–8	5.17[c] ±0.23	13.24[c] ±1.87	—[d]	29.99 ±5.66	0.78[c] ±0.32	49.18	61.38
		24–28	7.5–8	0.60 ±0.14	1.81 ±0.52	—	9.79	—		
Female (3)[e]	40	0–24	7	3.42 ±0.46	20.51 ±2.80	—	33.67[f] 37.32	2.81[f] 3.30	62.28	70
		24–48	7	0.63 ±0.15	2.56 ±0.76	—	4.29	—		
Rats										
Male (5)	35	0–24	8–9	5.95[c] ±1.56	23.13[c] ±3.85	0.36 ±0.10	16.07 ±3.82	4.10[c] ±0.65	49.25	53.18
		24–48	8.5–9	0.13 ±0.03	1.57 ±0.24	0.38 ±0.08	2.08 ±0.53	0.15 ±0.08		
Female (5)	35	0–24	6.5–9.5	15.25 ±4.40	12.53 ±1.68	0.00	12.34 ±5.33	12.06 ±1.42	52.18	56.52
		24–48	8–9	0.45 ±0.11	2.08 ±0.37	0.11 ±0.07	1.35 ±0.73	0.46 ±0.05		
Guinea pigs										
Male (2)	70	0–24	7.0–8.5	0.89	7.78	1.06	16.40	1.12	26.19	27.49
				1.45	14.47	0.00	20.38	1.50	37.78	42.60
		24–48	7–9	0.54	0.23	1.22	0.53	0.00		
				1.14	2.67	0.00	0.83	0.18		
Male (3)	35	0–24	6.5–8.5	1.40 ±0.59	10.09[c] ±2.06	3.84 ±1.95	16.21 ±5.75	1.25 ±0.71	28.86	29.91
		24–48	8–9	0.12 ±0.07	0.56 ±0.33	0.78 ±0.41	0.36 ±0.31	0.01 ±0.01		
Guinea pigs, female (4)	35	0–24	7–8.5	2.19 ±0.14	4.45 ±0.66	0.45 ±0.15	40.55 ±8.14	3.37 ±0.49	50.56	55.02
		24–48	7–9	0.61 ±0.11	1.65 ±0.66	0.21 ±0.11	1.64 ±0.34	0.56 ±0.12		
Rabbits										
Male (1)	35	0–24	7	0.32	2.17	0.26	18.22	21.45	42.21	53.42
		24–48	8.5	0.12	2.16	0.19	3.69	5.24		
Male (1)	35	0–72	8.0	0.06	2.65	0.13	6.34	14.39	23.44	23.96
		72–96	8.5	0.01	0.17	0.00	0.19	0.15		
Female (2)	35	0–24	7.5–9	0.02	0.20	0.00	0.30	0.53	1.05	15.58
				0.04	0.36		1.80	3.00	4.84	34.63
		24–72	8–9	0.05	0.71	0.14	4.27	5.45		
				0.09	8.47	0.32	12.78	12.07		
Cats										
Male (2)	20	0–24	6.5–7	3.13	3.13	2.23	46.56	0.90	53.72	60.1
				13.62	7.57	2.74	55.76	2.21	79.16	91.1
		24–48	6.5	0.19	1.40	—	4.79	0.00		
				0.20	3.37	—	8.26	1.08		
Female (2)	20	0–24	7	6.04	3.91	2.33	52.74	0.26	62.95	91.7
				9.52	4.04	3.20	58.46	1.78	73.80	102.8
		24–48	6.5	0.89	2.47	0.45	25.17	0.21		
				1.37	5.41	0.48	22.00	0.24		
Dogs										
Male (1)	20	0–24	7	0.15	1.77	0.35	73.91	1.48	75.54	84.70
		24–48	7	0.00	0.47	—	6.92	0.00		
Female (1)	20	0–24	7.5	0.20	2.06	0.32	69.08	1.18	72.32	80.85
		24–48	7	0.00	1.18	0.19	7.15	0.00		

[a] Measures of variance where shown are ± SE. [b] Twenty-eight male mice were divided into three groups of 10, 10, and eight. [c] Significantly different from the females at $p < 0.05$ level. [d] Dashes indicate amounts below detectable limits. [e] Twenty-one female mice were divided into three groups of seven each. [f] The urine of the third group was insufficient for determination.

rabbits were deprived of food for 24 hr following drug administration, but water was given *ad libitum*. Urine was collected 24 hr prior to drug administration (control) and 0–24 and 24–48 hr after drug administration. After the pH and volume were measured, all urine was frozen until drug analysis.

Determination of Meperidine and Its Metabolites—Meperidine, p-hydroxymeperidine, normeperidine, and meperidinic and normeperidinic acids were determined with a GLC procedure previously described (26). With lidocaine as the internal standard, free drugs were extracted with ether from the urine adjusted to pH 10. Upon evaporation of the extract to dryness, the residues were derivatized with trifluoroacetic anhydride. After removal of the excess derivatizing agent, the residue was dissolved in 50 μl of ethyl acetate (dried over calcium hydride), and 1 μl was injected into a gas–liquid chromatograph equipped with a Poly I-110 (1.8 m × 2 mm) column and flame-ionization detector.

Total (free and conjugated) meperidinic and normeperidinic acids were determined as meperidine and normeperidine, respectively, after the sample was treated with ethanol–sulfuric acid. Meperidine and its metabolites were extracted from the urine as the free base but were converted to the percent equivalent of administered dose.

RESULTS AND DISCUSSION

Urinary excretion of meperidine and its metabolites in mice, rats, guinea pigs, rabbits, cats, and dogs is presented in Table I. The amount of meperidine (Fig. 1) observed in the urine of mice, rats, guinea pigs, and cats was significantly higher than that in the urine of rabbits and dogs. The amount of meperidine in the urine of mice, rats, guinea pigs, and cats was comparable to that of humans (1–9) and monkeys (10). This observation appears to correlate well with meperidine analgesia reported between species. Normeperidine, p-hydroxymeperidine (except in the mice), and total meperidinic and normeperidinic acids were observed in all species studied; these metabolites also were reported in humans (7, 13).

Urinary pH affects excretion of meperidine and its metabolites in humans (6, 7). Urine acidification increases the excretion of meperidine

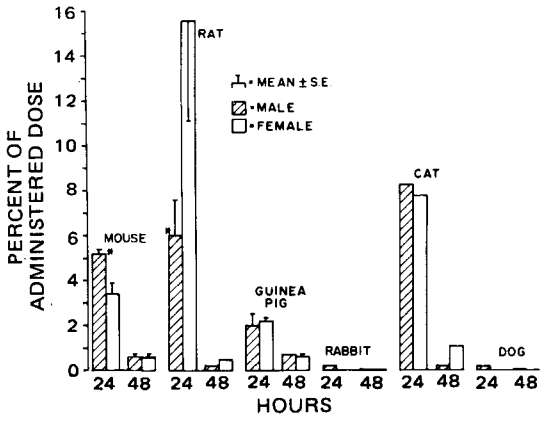

Figure 1—*Urinary excretion of meperidine in the mouse, rat, guinea pig, rabbit, cat, and dog after intraperitoneal administration of meperidine. The asterisk (*) indicates significantly different from the female at* $p < 0.05$ *level.*

and normeperidine, whereas very little of these compounds is excreted in alkaline urine. The recovery of meperidine and its metabolite, normeperidine, from 10 patients whose urinary pH was maintained at 4.8–5.25 varied between 10 and 50 and 2 and 20%, respectively, of the administered dose. However, 1% of the administered dose was excreted in subjects whose urinary pH was maintained at >7.0. In the present study, the urinary pH of animals was not controlled. The physiological urinary pH of dogs and rabbits appeared in the same range as the other species studied. Therefore, the small amount of meperidine and normeperidine found in the dog and rabbit urine appears to be a metabolic effect and not due to urinary pH.

The results indicate that all species studied have the capacity to *N*-demethylate meperidine to normeperidine (Fig. 2) and to hydrolyze meperidine and normeperidine to their respective acids (Figs. 3 and 4). With the exception of mice, meperidine excretion tended to be less in males than in females, and normeperidine and the sum of normeperidine and normeperidinic acids excretion tended to be greater. These data are consistent with the male having a higher *N*-demethylating activity than the female, with the exception of mice (27, 28). The present data on *in vivo* meperidine metabolism between male and female rats also correlate well with those obtained in *in vitro* studies (29).

The higher amount of normeperidine in the urine of mice, rats, and guinea pigs than in the urine of rabbits, cats, and dogs may reflect the further metabolism of normeperidine in the latter species.

Although conjugated *N*-hydroxynormeperidine was identified in the urine of rats and guinea pigs (14), *N*-hydroxynormeperidine was not determined in the present study because the pure standard was not available. Under the conditions for the determination of conjugated meperidinic and normeperidinic acids, *N*-hydroxynormeperidine probably was converted to normeperidine and measured as such or it decomposed.

The amount of meperidinic acid excreted in the urine of both sexes of the mouse, rat, guinea pig, cat, rabbit, and dog did not appear to be significantly different, suggesting that the esterase activity in both sexes may be equal. The ratios of meperidine to normeperidine excreted in 48

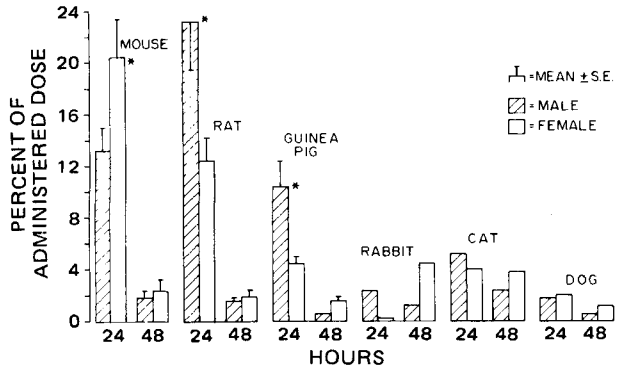

Figure 2—*Urinary excretion of normeperidine in the mouse, rat, guinea pig, rabbit, cat, and dog after intraperitoneal administration of meperidine. The asterisk (*) indicates significantly different from the female at* $p < 0.05$ *level.*

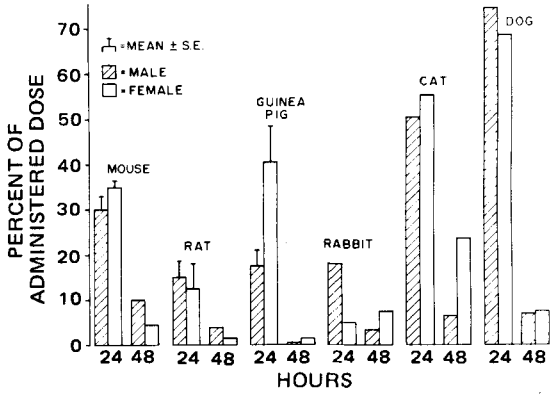

Figure 3—*Urinary excretion of total meperidinic acid in the mouse, rat, guinea pig, rabbit, cat, and dog after intraperitoneal administration of meperidine.*

hr in both sexes were less than one, whereas the ratios of total meperidinic acid to total normeperidinic acid ranged from 10 to 65. These data suggest that meperidine may be metabolized more extensively than its metabolite, normeperidine. The normeperidinic acid ought to be derived from normeperidine since meperidinic acid does not undergo *N*-demethylation to normeperidinic acid (4). Similarly, it was observed that morphine was metabolized more extensively than normorphine in dogs (30).

p-Hydroxymeperidine, a metabolite with mild analgesic effects, was observed in the urine of all species studied except mice (Table I). Free *p*-hydroxymeperidine varied among species and between sexes and accounted for 0.1–4% of the administered dose (Fig. 5). Conjugated *p*-hydroxymeperidine was not determined because the procedure is not optimal for its determination.

In one study in male guinea pigs, the dose of meperidine in one group of animals was twice that in the other. The urinary excretion profile between the two groups did not appear different.

The dogs and cats excreted 80–100% of the administered dose as total drug in the 48-hr urine; the other species excreted 16–60% of the dose. From 80 to 90% of the excreted drug was found in the 24-hr urine. This finding confirms the observation of Way *et al.* (3) that after meperidine administration to rats three times daily for several days, virtually no drug could be recovered from the animals 24 hr later. The amount unaccounted for could be due to *N*-hydroxy- and *p*-hydroxynormeperidine and metabolites excreted in the feces. Significant amounts of radioactivity have been found in the large intestine and feces of rats administered *N*-^{14}C-labeled meperidine (11). Gastric and biliary excretion of meperidine in humans also was observed (31).

Meperidine induces analgesia in mice (15–18), rats (19, 20), guinea pigs (21), cats[7] (22), and humans (23), and some intact meperidine was observed in the urine of these species. In the dog, a large dose (which produces toxic effects) is needed to induce mild analgesic effects (24, 25). Very little meperidine was observed in the dog urine. Meperidine could be substituted for morphine in the morphine-dependent monkey[8] and humans (23) but not in dogs (24, 25).

The small amount of meperidine and normeperidine observed in the

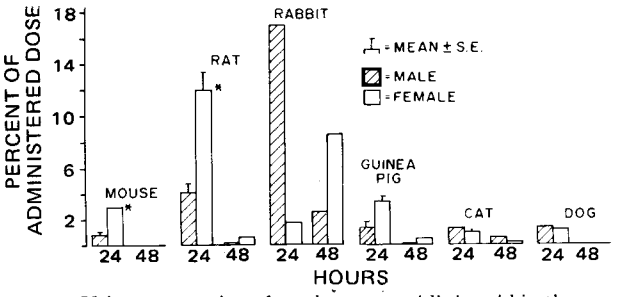

Figure 4—*Urinary excretion of total normeperidinic acid in the mouse, rat, guinea pig, rabbit, cat, and dog after intraperitoneal administration of meperidine. The asterisk (*) indicates significantly different from the male at* $p < 0.05$ *level.*

[7] R. G. Babington, T. L. Waldron, and P. W. Wedeking, reported to the Committee on Problems of Drug Dependence, 1968, p. 5570.

[8] G. Deneau, D. McCarthy, and M. H. Seevers, reported to the Committee on Drug Addiction and Narcotics, 1959, p. 2057.

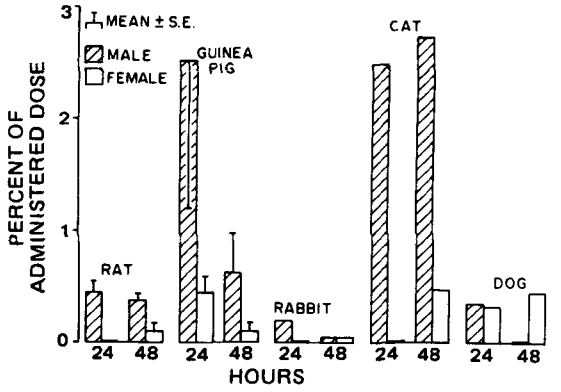

Figure 5—*Urinary excretion of* p*-hydroxymeperidine in the rat, guinea pig, rabbit, cat, and dog after intraperitoneal administration of meperidine.*

urine of rabbits and dogs is consistent with the mild analgesic effects of the drug in dogs. This finding suggests that these two species metabolize meperidine faster than other species, which is supported by the work of Peters *et al.* (10) on the hypothermic effect and urinary excretion of meperidine among strains of monkeys and the plasma half-life of meperidine in dogs, humans, and monkeys. These researchers reported that the median analgesic dose of meperidine in the squirrel monkey (8.0 mg/kg) was ~2.3 times that in the rhesus monkey (3.5 mg/kg) (10). Rhesus monkeys excreted substantially higher fractions of the dose as meperidine than did squirrel monkeys. On the other hand, squirrel monkeys excreted a threefold higher fraction of the dose as normeperidine than did the rhesus monkeys. This result indicates that the squirrel monkey metabolizes meperidine faster than the rhesus monkey. The plasma half-lives of meperidine in humans and monkeys are 3.0 and 1.8 hr, respectively[9] (32–34), significantly longer than the plasma half-life (0.5 hr) in the dog (4, 35).

Among the metabolites, normeperidine and *p*-hydroxymeperidine were reported to have analgesic effects with low potency (15, 16, 19), whereas meperidinic and normeperidinic acids had no analgesic effects (4). The potency ratio between meperidine and normeperidine in mice was 1:0.7 (15, 16), whereas the ratio between meperidine, normeperidine, and *p*-hydroxymeperidine in rats on a molar basis was 1:0.33:0.07 (19). If the amount of meperidine and normeperidine excreted in the urine reflects the relative amount of meperidine and normeperidine present in the body and brain, it is possible that normeperidine plays a role in the analgesic effect of meperidine because of its relatively high analgesic potency and high percentage excretion. The relationship between meperidine analgesia and the brain concentration of meperidine and normeperidine in different species administered varying doses of the drug by different routes requires further study.

In summary, after intraperitoneal administration of 20–40 mg of meperidine hydrochloride/kg to mice, rats, guinea pigs, cats, and dogs, >90% of the excreted drugs was found in the 24-hr urine. The amounts of meperidine observed in the urine of mice, rats, guinea pigs, and cats were significantly higher than those observed in the rabbits and dogs. This observation appears to correlate well with the meperidine analgesia reported in these species. Normeperidine, *p*-hydroxymeperidine (except in the mice), and total meperidinic and normeperidinic acids were observed in all species. All species studied have the capacity to *N*-demethylate meperidine to normeperidine and to hydrolyze meperidine and normeperidine to their respective acids. The male has a higher *N*-demethylating activity than the female, with the exception of mice. Ester hydrolysis is a major metabolic pathway for metabolism of meperidine.

[9] G. A. Deneau and K. Nakai, National Research Council–National Academy of Sciences Report to the Committee on Drug Addiction and Narcotics, 1961, p. 2460.

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