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TLC Identification and GLC Determination of Meperidine and Its Metabolites in Biological Fluids

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Abstract □ Procedures were developed for TLC identification and GLC determination of meperidine and its metabolites, *i.e.*, *p*-hydroxymeperidine, normeperidine, and meperidinic and normeperidinic acids. Meperidine, *p*-hydroxymeperidine, and normeperidine were extracted with ether from biological fluids at pH 10, whereas meperidinic and normeperidinic acids and conjugated metabolites remained in the aqueous phase. The residue, upon evaporation of the extract to dryness, was derivatized with trifluoroacetic anhydride and gas chromatographed. Total (free and conjugated) meperidinic and normeperidinic acids in the aqueous phase were converted and determined as meperidine and normeperidine, respectively. A preliminary result of urinary disposition of meperidine and its metabolites in the rat is presented. The identity of these metabolites was confirmed with GLC–mass spectrometry.

Keyphrases □ Meperidine—and metabolites, TLC identification and GLC determination in biological fluids, rat, dog, and human □ Metabolites—meperidine, TLC identification and GLC determination in biological fluids of rat, dog, and human □ TLC—identification of meperidine and metabolites in biological fluids of rat, dog, and human □ GLC–mass spectrometry—determination of meperidine and metabolites in biological fluids of rat, dog, and human

The known major metabolites of meperidine are normeperidine and meperidinic and normeperidinic acids (1–4); *p*-hydroxymeperidine (5), meperidine *N*-oxide (6), hydroxymethoxymeperidine (7), *N*-hydroxynormeperidine (7), and *p*-hydroxynormeperidine[1] are minor metabolites (Scheme I). The hydrophilic and hydroxylated metabolites are excreted mainly in conjugated forms (1–3, 5, 7).

In earlier studies, radioisotopic and methyl orange dye methods (1–3, 8) were used to estimate meperidine and normeperidine in biological fluids. In later studies, meperidine, normeperidine, and *p*-hydroxymeperidine were estimated by GLC or GLC–mass spectrometry (9–19). Total meperidinic and normeperidinic acid were estimated as meperidine and normeperidine by methyl orange, GLC, and GLC–mass spectrometric methods after esterification (1–4, 9–20). This paper presents a simpler and more sensitive method for the determination of meperidine and its metabolites in biological fluids, primarily using GLC.

EXPERIMENTAL

Drugs—Meperidine hydrochloride[2], [*N-methyl*-^{14}C]meperidine hydrochloride[3] (3.4 mCi/mmole), normeperidine hydrochloride[2], *p*-hydroxymeperidine[4], and lidocaine hydrochloride[5] were used. The purity of the radiolabeled meperidine, determined by TLC with three solvent systems, was at least 98%. [*N-methyl*-^{14}C]Meperidinic, meperidinic, and normeperidinic acids were obtained by alkaline hydrolysis of their respective esters, and their purity was found to be 98% by TLC and GLC–mass spectrometry.

Meperidine *N*-oxide was synthesized by oxidation of meperidine (100 mg) by adding 85% *m*-chloroperbenzoic acid[6] (150 mg) in dried ether (2 ml) dropwise over 5 min. After the addition was completed, the solution was left at room temperature for 2 hr. Upon removal of the solvent, the residue was suspended in 2 ml of 10% potassium carbonate solution and extracted with ethylene dichloride containing 30% isopropyl alcohol (3 × 10 ml). Crystals were obtained upon concentration of the extract to ~1 ml. After cooling, centrifugation, and aspiration of the final drops of extract, the crystals were washed with ether and dried under vacuum, yielding 99 mg.

N-Hydroxynormeperidine was synthesized by oxidation of normeperidine with *m*-chloroperbenzoic acid (7). The final product was contaminated with normeperidine and other by-products but was sufficient for TLC and GLC–mass spectrometric identification.

GLC—The chromatograph[7] was equipped with flame-ionization detectors and 182-cm × 2-mm glass columns packed with 3% Poly I-110 coated on 80–100-mesh Gas Chrom Q. The temperatures of the oven, injector, and detector were 205, 225, and 250°, respectively. The gas flow rates of nitrogen, hydrogen, and compressed dry air were 30, 30, and 400 ml/min, respectively.

GLC–Mass Spectrometry—Chemical-ionization mass spectral data were obtained on a gas chromatograph–mass spectrometer[8] equipped with an interactive data system[9] and a 182-cm × 2-mm glass column packed with 3% Poly I-110 coated on 80–100-mesh Gas Chrom Q. The temperatures of the injector, column, and ion source were 230, 210, and 100°, respectively. Other specifications of the mass spectrometer were described previously (21).

TLC—Standard TLC procedures were followed. Aliquots (50 μl) of methanolic solution containing 50 μg of meperidine or its metabolites were spotted on instant thin-layer silica gel sheets[10] and linear, precoated glass silica plates[11]. Chromatograms were developed with one of the following solvent systems: A, *n*-butanol–water–acetic acid (35:10:3); B, ethyl acetate–ammonium hydroxide (17:1); C, ethyl acetate–methanol–ammonium hydroxide (17:2:1); D, benzene–methanol–diethylamine (48:1:1); E, *n*-butanol–3% ammonium hydroxide in water (50:50) using the upper phase; and F, ethyl acetate–diethylamine (17:1).

The chromatogram of nonlabeled standards was sprayed with iodo-

[1] Unpublished observations.
[2] Sterling-Winthrop Pharmaceutical Co., Rensselaer, N.Y.
[3] Mallinckrodt Chemical Co., St. Louis, Mo.
[4] Professor C. Lindberg, Department of Organic Pharmaceutical Chemistry, University of Uppsala, Uppsala, Sweden.
[5] Astra Pharmaceutical Products, Worcester, Mass.
[6] Practical grade, Aldrich Chemical Co., Milwaukee, Wis.
[7] Model 2700, Varian Aerograph, Varian Associates, Palo Alto, Calif.
[8] Model 3300, Finnigan Corp., Sunnyvale, Calif.
[9] Model 6000, Finnigan Corp., Sunnyvale, Calif.
[10] Gelman Instrument Co., Ann Arbor, Mich.
[11] Quantum Industries, Fairfield, N.J.

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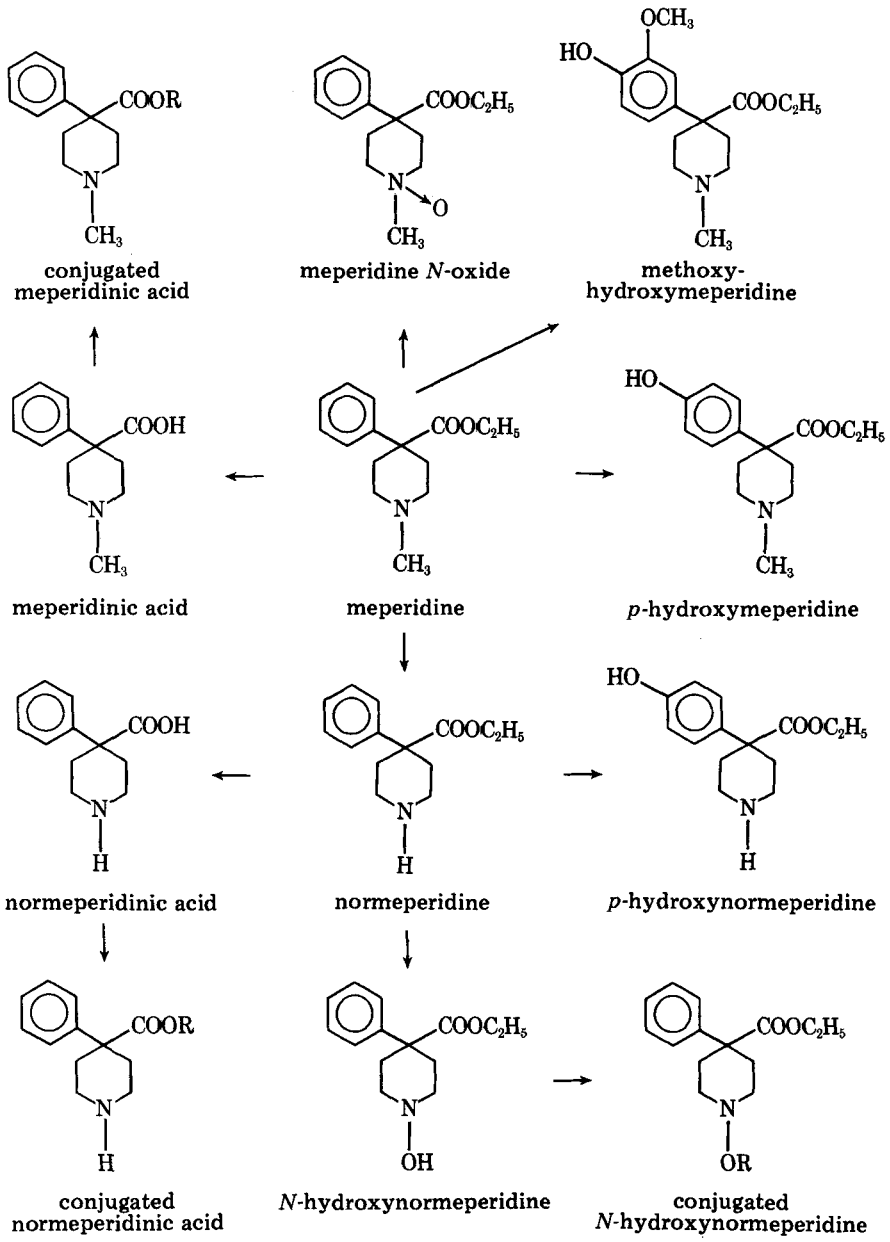

Scheme I—Metabolic pathways of meperidine.

platinate or ammonia–silver nitrate (for *n*-hydroxynormeperidine). The radiochromatogram of [*N-methyl*-^{14}C]meperidinic acid was analyzed by placing each strip (obtained by cutting the sheet into 1-cm strips) in a liquid scintillation vial, swirling with 0.5 ml of methanol, and counting with 10 ml of Bray's solution[12] in a liquid scintillation spectrometer[13].

Determination of Meperidine, *p*-Hydroxymeperidine, and Normeperidine in Urine—One-half to 2 ml of urine, water (to make up a total volume of 2 ml), and 0.1 ml of lidocaine hydrochloride solution (0.2 mg/ml, an internal standard) were placed in a 15-ml stoppered centrifuge tube, adjusted to pH 10 with 0.1 ml of concentrated ammonium hydroxide, and extracted twice with 5 ml of ether by shaking each time at 280 oscillations/min for 10 min and centrifuging for 5 min. The extract was transferred without the aqueous phase to an acylation tube and evaporated to dryness under a nitrogen stream at room temperature. Upon evaporation of the ethereal extract to dryness, the residue was used for TLC identification and GLC determination of free meperidine, *p*-hydroxymeperidine, and normeperidine.

The aqueous phase was used to determine total meperidinic and normeperidinic acids and conjugated *p*-hydroxymeperidine.

For GLC determination, the residue was derivatized with 0.1 ml of trifluoroacetic anhydride by heating the mixture in an ethylene glycol bath at 60° for 10 min. After evaporation of the excess derivatizing agent by a nitrogen stream at room temperature, dried ethyl acetate (50 μl) was added; 1 μl of the solution was injected into the gas chromatograph. Calibration curves at the peak height ratio (compound to internal standard) *versus* the concentration for meperidine, *p*-hydroxymeperidine, and normeperidine were linear (r = 0.99) over the range of 1–200 μg/2 ml. A concentration of meperidine, *p*-hydroxymeperidine, and normeperidine as low as 150 ng/2 ml of urine could be measured.

For studying the recovery of drugs from biological fluids, lidocaine was added to the residues of the ethereal extract prior to derivatization. The recovery was calculated from a comparison of the peak height ratio of extracted drug to lidocaine to that of unextracted drug to lidocaine.

Determination of Total Meperidinic and Normeperidinic Acids in Urine—After extraction of meperidine, normeperidine, and free *p*-hydroxymeperidine, the aqueous phase was evaporated almost to dryness (~0.1 ml) at 55° under reduced pressure with an evaporator[14] and then evaporated to complete dryness in a freeze drier. The residue was refluxed with 3 ml of absolute alcohol containing 10% sulfuric acid at 100° for 5 hr. This method hydrolyzed conjugated *p*-hydroxymeperidine and

[12] Bray's solution consists of naphthalene (60 g), 2,5-diphenyloxazole (4 g), 1,4-bis[2-(5-phenyloxazolyl)]benzene (200 mg), methanol (100 ml), ethylene glycol (20 ml), and dioxane to make 1 liter.

[13] Mark III, Searle Analytic, Des Plaines, Ill.

[14] Evaporator-mix, Buchler Instruments, Fort Lee, N.J.

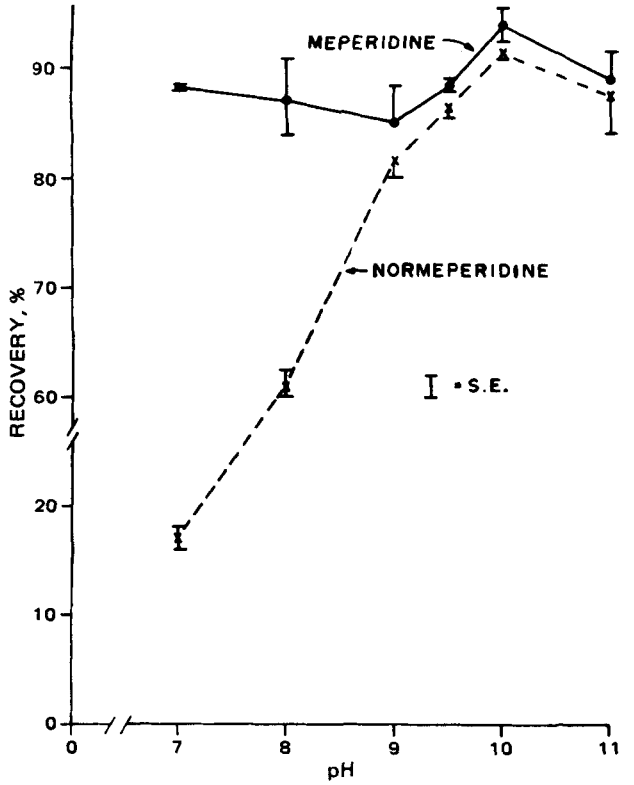

Figure 1—*Effect of pH on the recovery of meperidine and normeperidine. Meperidine (20 μg) and normeperidine (20 μg) from urine (2 ml) were extracted into the organic phase (6 ml of ether) by shaking for 10 min.*

meperidinic and normeperidinic acids to the free form; meperidinic and normeperidinic acids were esterified to meperidine and normeperidine, respectively.

The solution was reduced to ~0.3–0.5 ml (removal of ethanol) by evaporation at 55° under reduced pressure with an evaporator[14]. To the residue were added 1.0 ml of concentrated ammonium hydroxide (pH ~9–10) and 0.1 ml of lidocaine hydrochloride (0.2 mg/ml) solution. Then the solution was extracted with 6 ml of ether, and 5 ml of the extract was evaporated to dryness. The residue was derivatized with trifluoroacetic anhydride and determined by GLC. Calibration curves for both acids and *p*-hydroxymeperidine were linear (r = 0.98–0.99) in the concentration range of 10–200 μg/2 ml. Recoveries of water-soluble metabolites were only ~30–40%.

Determination of Meperidine and Its Metabolites in Blood and Plasma—The procedure for urine was modified slightly for determination of meperidine and normeperidine in plasma and blood. The plasma or blood (2 ml), including the internal standard, was adjusted to pH 10 and extracted with 8 ml of ether. After removal of the aqueous phase, 6 ml of the ethereal extract was shaken with 1 ml of 1 *N* HCl for 5 min and centrifuged for 5 min. The organic phase was carefully aspirated off without removal of any aqueous phase. The acidic aqueous phase was adjusted to pH 10 with 0.5 ml of concentrated ammonium hydroxide and extracted with 6 ml of ether. After centrifugation, 5 ml of the organic phase was transferred to an acylation tube and then treated as described for the determination of meperidine and normeperidine.

Pilot Experiment on Urinary Disposition of Meperidine in Rats—Meperidine hydrochloride (35 mg/kg) dissolved in saline was administered intraperitoneally to Wistar male rats housed individually in air-conditioned quarters (23°) with 12-hr light–dark cycles. Food and water were given *ad libidum*. 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 the time of drug analysis.

RESULTS AND DISCUSSION

Extraction and Recovery of Meperidine and Its Metabolites—[*N-methyl*-^{14}C]Meperidine hydrochloride was used to study some factors influencing meperidine recovery such as pH, solvent, number of extractions, salting, shaking time, and temperature on evaporation of the solvent extract. The mean recovery of [*N-methyl*-^{14}C]meperidine (2 μg) from aqueous solution was constant over pH 7–10 (Fig. 1) and was ~98.56 ± 2.14% (*SE*). The recovery of meperidine from solution at pH 9.5 by extraction with ether was ~20% greater than that with benzene, chloroform, or toluene extractions. The presence or absence of 0.5 g of sodium chloride appeared to make no difference in recovery. The meperidine recovery was inversely proportional to the length of the solvent evaporation time on a slide warmer[15] set at 50°; better results were obtained when the solvent was evaporated to dryness at room temperature under a nitrogen stream. There were no significant differences in recovery with 5, 10, or 15 min of shaking with 6 ml of ether at pH 9.5.

No appreciable radioactivity was extracted in the organic phase when [*N-methyl*-^{14}C]meperidinic acid (1–100 μg) in aqueous solutions at pH 10 was extracted. It is likely that normeperidinic acid also would not be extracted. However, it was reported (20) that meperidinic and normeperidinic acids could be extracted at pH 9–10 with ethylene dichloride, although this finding could not be confirmed.

Use of a resin column[16] for extraction of meperidinic and normeperidinic acids, with the eluate analyzed for meperidinic and normeperidinic acids and esterification at various steps, was investigated. However, no variations saved time or gave clearer extracts than the organic solvent extraction and determination from the aqueous phase described.

The optimum pH for recovery of normeperidine from aqueous solution determined (in triplicate) with GLC was at pH 10 (Fig. 1). The recovery of normeperidine added to the control urine was 95.79 ± 3.15% (*SE*).

The recovery of *p*-hydroxymeperidine added to the control urine was 101.83 ± 3.31%.

TLC Identification of Meperidine and Its Metabolites—The R_f values of meperidine and its metabolites developed with various solvent systems on both instant TLC sheets and silica gel plates are presented in Table I. Solvent System D appeared to be best for separation of meperidine and its metabolites on TLC silica gel plates. None of the systems using instant TLC sheets was satisfactory.

GLC Determination of Meperidine and Its Metabolites—Figure 2 shows the chromatogram of the extract of rat control urine with added internal standard after a single extraction and shows only a single peak of lidocaine (panel 1). The extract of control urine with added internal standard plus authentic standards showed peaks of meperidine, *p*-hydroxymeperidine, normeperidine, and lidocaine (panel 3) with retention times of 3.7, 4.1, 7.7, and 9.3 min, respectively. The retention times of these compounds varied slightly from column to column, but the sequence remained the same.

The chromatogram of the extract of the 0–24-hr rat urine extracted for free drugs showed peaks with retention times corresponding to meperidine, *p*-hydroxymeperidine, and normeperidine and an unidentified peak with a retention time of 10.3 min (panel 4). The identity of meperidine and its metabolites was confirmed further with GLC–mass

Table I—R_f Values of Meperidine and Its Metabolites

Compound	Solvent System A	B	C	D	E	F
Instant Thin-Layer Silica Gel Sheet[a]						
Meperidine	1.00	1.00	1.00	1.00	1.00	1.00
p-Hydroxymeperidine	1.00	1.00	1.00	1.00	1.00	1.00
Meperidine *N*-oxide	1.00	0.37	0.93	0.33	1.00	1.00
Meperidinic acid	1.00	0.00	0.00	0.29	1.00	0.22
Normeperidine	1.00	1.00	1.00	1.00	1.00	1.00
N-Hydroxynormeperidine	1.00	1.00	0.95	0.90	1.00	1.00
Normeperidinic acid	0.00	NV[b]	NV	NV	NV	NV
Thin-Layer Silica Gel Plates[c]						
Meperidine	0.47	0.87	0.85	0.71	0.69	0.79
p-Hydroxymeperidine	0.45	0.55	0.72	0.17	0.66	0.40
Meperidine *N*-oxide	0.50	0.03	0.25	0.04	0.43	0.19
Meperidinic acid	0.37	NV	NV	0.00	0.28[d]	0.18
Normeperidine	0.60	0.38	0.56	0.24	0.46	0.33
N-Hydroxynormeperidine	0.85	0.73	0.84	0.44	0.30	0.67
Normeperidinic acid	0.48[e]	NV	NV	NV	0.20[d]	NV

[a] Gelman Instrument Co., Ann Arbor, Mich. [b] NV = not visible. [c] Quantum Industries, Fairfield, N.J. [d] Gray spot. [e] Spot was seen overnight after spraying.

[15] Fisher Scientific Co.
[16] Amberlite XAD-2, Brinkmann Instrument Co., Westbury, N.Y.

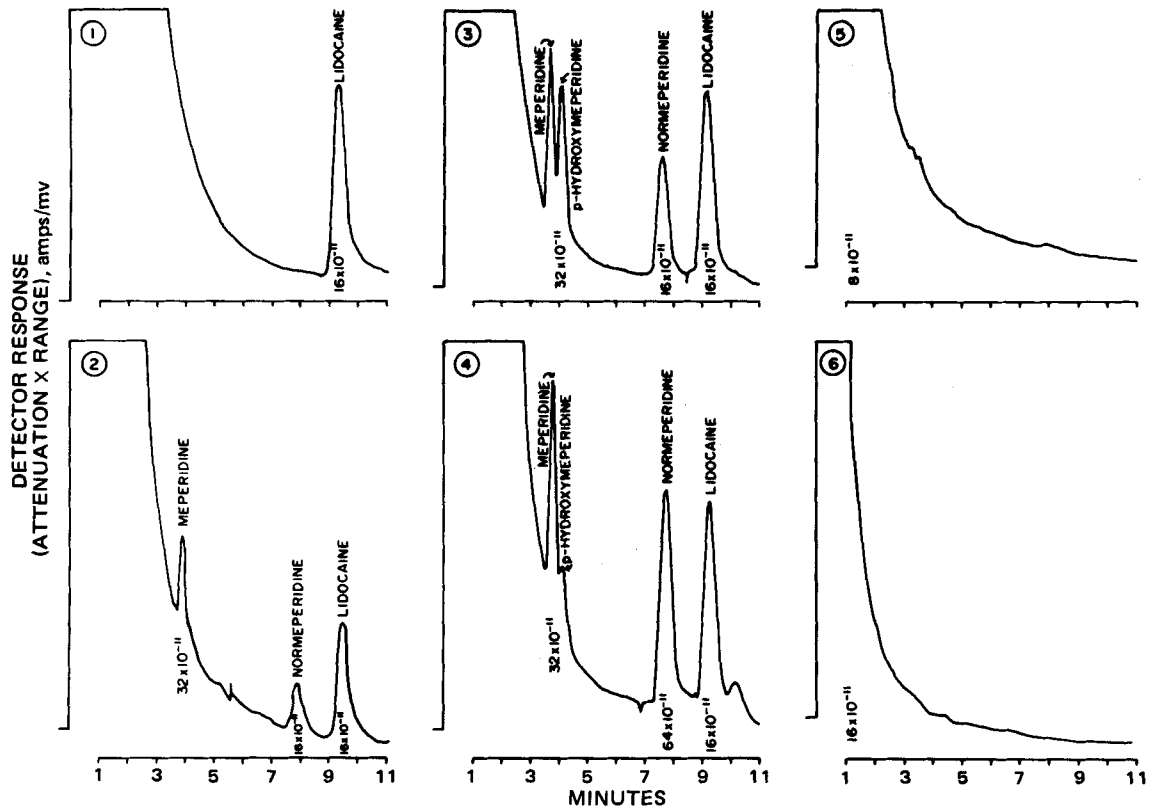

Figure 2—*Chromatograms of the extracts. Key: 1, control urine of rat with added lidocaine; 2, aqueous phase of the rat urine after ether extraction and sulfuric acid ethanol treatment with added lidocaine; 3, control urine of rat with added authentic standards; 4, urine of rat administered meperidine with added lidocaine; 5, control plasma of a dog; and 6, control plasma of a man.*

spectrometry. The chromatogram shown in panel 2 was obtained from the extract for determination of conjugated *p*-hydroxymeperidine and total meperidinic and normeperidinic acids. It showed peaks with retention times corresponding to meperidine and normeperidine, which were converted from free and conjugated meperidinic and normeperidinic acids, respectively. A peak of *p*-hydroxymeperidine appeared in the chromatogram of the extract of free drugs but not of the conjugated drugs, indicating that acid hydrolysis is not optimal for the determination of conjugated *p*-hydroxymeperidine.

The chromatogram of the extract obtained from normal dog plasma after one extraction showed no interfering peaks (panel 5). The chromatogram of the extract of human plasma and blood showed small peaks that interfered with the peaks of meperidine and *p*-hydroxymeperidine. The peak height of the interfering peak obtained from 2 ml of human plasma or blood corresponded to ~150 ng of meperidine. After a triple reverse extraction, the interfering substances were eliminated (panel 6).

The GLC determination of meperidine and normeperidine is similar to, but simpler than, that reported by Klotz *et al.* (12) since the extraction of derivatized normeperidine (as trifluoroacetamide) from aqueous solution is eliminated. For determination of meperidinic and normeperidinic acids, the procedure is similar to, but more sensitive than, that reported by Wainer and Stambaugh (4) by derivatization of normeperidine with trifluoroacetic anhydride.

Several GLC columns were investigated. The Poly I-110 column appeared to be more sensitive for the determination of normeperidine (as trifluoroacetamide) than 3% OV-17 and 3% SE-30 columns, although it appeared no different for the determination of meperidine.

Chlorophenylamine hydrochloride and diphenhydramine hydrochloride have been used as internal standards in the GLC analysis of meperidine. In this GLC system, they had a retention time considerably longer than lidocaine.

GLC–Mass Spectrometric Identification of Meperidine Metabolites in Rat Urine—The total ion current chromatogram and mass spectra of the extract (as trifluoroacetyl derivatives) of the unhydrolyzed urine of a male rat administered meperidine is shown in Fig. 3. The chromatogram showed peaks with retention times corresponding to authentic meperidine (spectrum 47), *p*-hydroxymeperidine (spectrum 56), normeperidine (spectrum 117), and lidocaine (spectrum 146). The fragmentation patterns of these peaks were identical to those of the authentic standards (Table II).

Since the peak (spectrum 56) with a retention time corresponding to that of *p*-hydroxymeperidine was small, a limited chromatogram at *m/z* 360 (M + 1 ion of trifluoroacetylated *p*-hydroxymeperidine) was recorded to confirm the existence of this mass; this technique only shows the peaks with mass equal to 360. The chromatogram showed a major peak at the retention time (spectrum 57) corresponding to that of the small peak appearing in the integrated total ion current chromatogram and a small peak (spectrum 117), due to the isotope mass of *m/z* 358, corresponding to that of normeperidine. The fragment pattern of the peak at spectrum

Table II—GLC and Chemical-Ionization GLC–Mass Spectral Characteristics of Standard Meperidine Metabolites and Extract from Urine of a Rat Administered Meperidine Hydrochloride, 35 mg/kg

Sample	Derivative	GLC R_t, min	GLC–Mass Spectrometry $(M-F^a)^+$	GLC–Mass Spectrometry $(M+1)^+$	*m/z* $(M+29)^+$	Other Prominent Ions		Identification
Meperidine	—	3.7	—	248 (100)[b]	276 (88)	202 (15)	174 (27)	—
p-Hydroxymeperidine	Trifluoroacetyl	4.1	340 (10)	360 (100)	388 (17)	—	—	—
Normeperidine	Trifluoroacetyl	7.7	310 (40)	330 (100)	358 (50)	256 (100)	284 (12)	—
Extract of rat urine	Trifluoroacetyl	3.7	—	248 (100)	276 (73)	202 (12)	174 (23)	Meperidine
		4.1	340 (10)	360 (100)	388 (17)	—	—	*p*-Hydroxymeperidine
		7.7	310 (80)	330 (100)	358 (90)	256 (100)	284 (22)	Normeperidine

[a] F = fluoride ion. [b] Percentage of relative intensity.

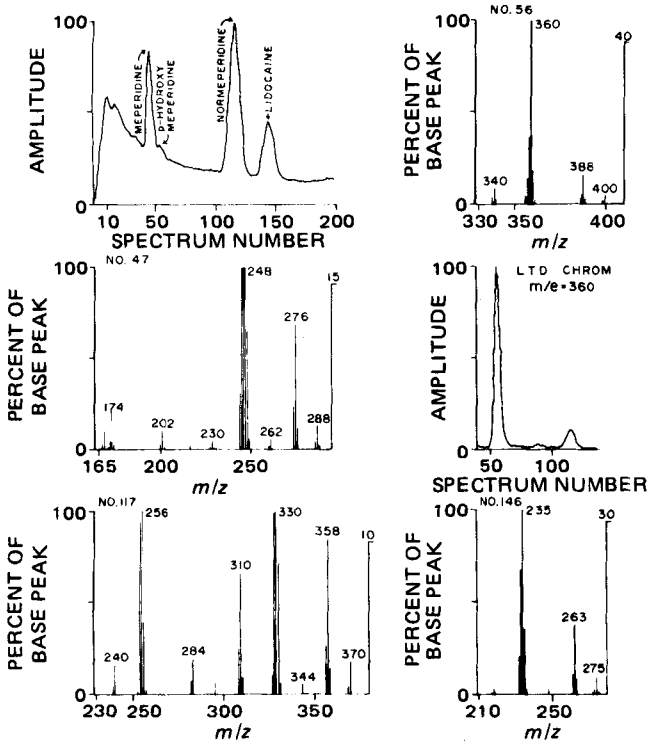

Figure 3—*GLC–mass spectrometric chromatogram, as trifluoroacetyl derivatives, of the 24-hr urinary extract of a rat administered meperidine. Key: upper left, integrated total ion current chromatogram; middle right; limited chromatogram at m/z 360; spectrum 47, meperidine; spectrum 56, p-hydroxymeperidine; spectrum 117, normeperidine; and spectrum 146, lidocaine (added internal standard).*

56 showed *m/z* 388 $(M + 29)^+$, 360 $(M + 1)^+$, and 340 $(M -$ fluoride ion$)^+$. The identity of *p*-hydroxymeperidine and normeperidine as metabolites thus was established and confirmed the observation of Lindberg *et al.* (5) that *p*-hydroxymeperidine is a metabolite of meperidine in the rat.

Urinary Excretion of Meperidine and Its Metabolites in Rats—A preliminary determination of the urinary excretion of meperidine and its metabolites in the rat indicated meperidine (6.1%), *p*-hydroxymeperidine (0.36%), total meperidinic acid (16.1%), normeperidine (24%), and total normeperidinic acid (3.9%) of administered meperidine hydrochloride (35 mg/kg). A detailed study of the urinary disposition of meperidine and its metabolites in several mammalian species will be reported in a separate paper.

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Electrokinetic Studies of Magnesium Hydroxide

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Abstract □ The electrophoretic mobility of magnesium hydroxide was studied as a function of the concentration of its potential-determining ions, namely, of the magnesium ions, and of the hydroxide ions or pH. The zero point of charge was located at ~10.8. The ζ-potential of magnesium hydroxide below this pH was positive. The addition of magnesium nitrate to magnesium hydroxide suspensions increased the positive ζ-potential and lowered the pH. The low solubility of magnesium hydroxide in water prevented the attainment of substantial concentrations of magnesium ions in solution. Increasing the hydroxide-ion concentration or the pH produced charge inversion. The largest negative ζ-potential was attained at pH 11.5. Further increases in pH produced no significant increase in the negative value of the ζ-potential.

Keyphrases □ Magnesium hydroxide—electrophoretic mobility in aqueous solution □ Electrophoretic mobility—magnesium hydroxide in aqueous solution □ Zero point of charge—magnesium hydroxide

Even though magnesium hydroxide suspensions are used extensively as antacids and laxatives, the information available on their electrokinetic properties is meager. Two sets of limited data, based on electro-osmosis and electrophoresis, were published in 1917 and 1934, respectively, for magnesium hydroxide that was precipitated with little

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