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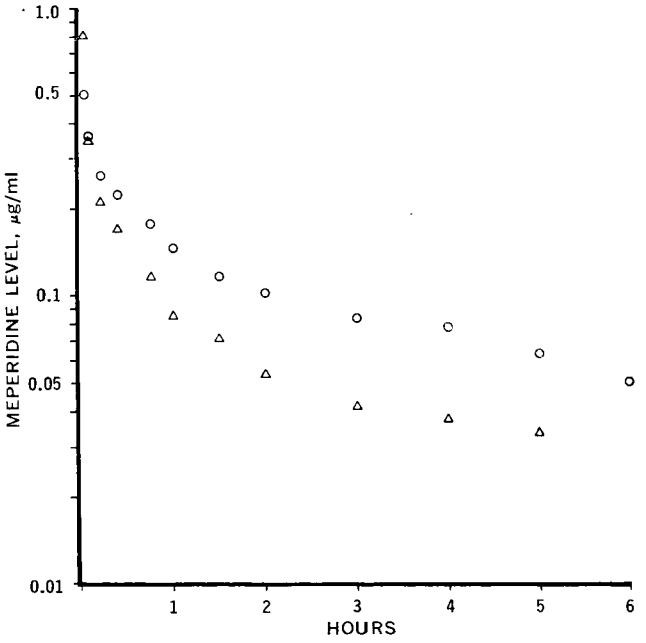

Figure 1—*Representative plasma concentration–time profiles following the intravenous injection of 50 mg meperidine hydrochloride. Key: ○, venous plasma, Subject L.M., dose corresponding to 0.74 mg/kg; and △, arterial plasma, Subject D.C., dose corresponding to 0.37 mg/kg.*

Meperidine and Other Basic Drugs: General Method for Their Determination in Plasma

Keyphrases □ Meperidine (and other basic drugs)—GLC analysis of plasma samples □ Amine drugs (basic)—GLC analysis of plasma samples □ GLC—analysis, meperidine and other basic drugs

Sir:

In a recent paper, Goehl and Davison (1) reported a GLC technique for the determination of meperidine in blood plasma. The method was used to determine plasma drug concentration *versus* time curves in dogs following administration of 15–25 mg/kg iv and yielded a limit of sensitivity of around 0.1 μg/ml.

We wish now to describe a method for the determination of meperidine, which is generally applicable to basic amine drugs. A similar procedure was reported by Hodshon *et al.* (2) for the determination of ketamine in plasma. This procedure allows the determination of clinically encountered low concentrations of meperidine for at least 6 hr following intravenous injection of 0.35–1.0 mg/kg and is currently being used to evaluate the effects of various anesthetic protocols on the kinetics of meperidine in man. Representative concentration *versus* time profiles are depicted in Fig. 1.

In the general method, the sample aliquot (usually 1.0 ml) was mixed with the internal standard solution (usually 100 μl, usually 1.0 μg), made basic with sodium hydroxide solution (100 μl, 1 *M*), extracted with ether (3 ml) in a Teflon-lined, screw-capped centrifuge tube (15 ml) by stirring on a mixer[1] (30 sec), and the phases were separated by centrifugation (2000 rpm, 2 min). Following flash freezing in an acetone–carbon dioxide bath, the organic phase was decanted into a second tube containing hydrochloric acid solution (200 μl, 1 *M*) and the phases were mixed and separated as before.

The organic phase was discarded and the aqueous phase was heated to around 60° for several minutes in a water bath to remove the residual ether. It was then cooled and transferred to a conical tube[2] with Teflon-lined screw cap (1 ml), made basic with sodium hydroxide solution (200 μl, 2 *M*), and extracted with methylene chloride (25 μl). The phases were separated as before. Aliquots (2 μl) of the organic phase were withdrawn with a microliter syringe and injected directly into the gas chromatograph[3]. The glass column, 150 cm × 3.2 mm o.d., packed with 3% OV-17 on Gas Chrom Q (100–120 mesh) was operated at 180° with helium as the carrier gas at a flow rate of 22 ml/min. For meperidine (R_T 3.8 min), the internal standard was *N*-methyl-*N*-ethyllidocaine hydrochloride[4] (R_T 5.1 min). Concentrations were calculated from a previously constructed standard curve of peak height ratio of meperidine/internal

[1] Vortex.
[2] ReactiVial, Pierce Chemical Co.
[3] Varian 1200, equipped with flame-ionization detector.
[4] 2-Methylethylamino-2′,6′-acetoxylidide hydrochloride.

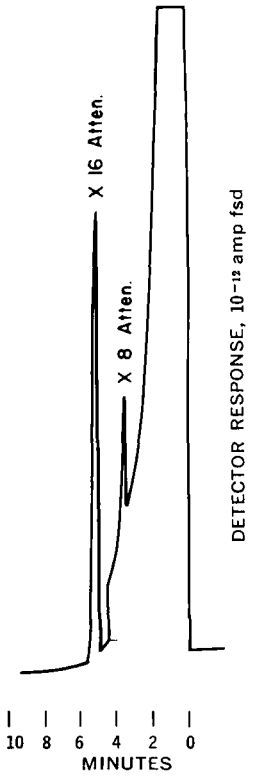

Figure 2—*Representative gas chromatogram obtained from a plasma sample containing 0.104 μg/ml meperidine (as base). Key: peak 1, meperidine (×8 attenuation); and peak 2, internal standard (×16 attenuation). Scale was expanded on first peak for more accurate measurement and to show lack of interference from other peaks.*

standard *versus* amount meperidine. The coefficient of variation of 2% was typical over the concentration range encountered. The limit of sensitivity attainable was approximately 0.005 μg/ml. A representative chromatogram is shown in Fig. 2.

Because procaine (and many ester-type local anesthetics) is susceptible to base-catalyzed hydrolysis with the general method, the following modifications were found useful. The plasma samples (previously treated with sodium arsenite to prevent enzymic hydrolysis) were made basic, where appropriate, with sodium carbonate solution (2 *M*, saturated with sodium chloride). Saturation with sodium chloride assisted the partition into the organic phase at the lower pH of the sodium carbonate (where the tertiary amine is still appreciably ionized). Final extraction was best accomplished with chloroform, which increased the partition of the basic drug.

The technique presented here offers the following advantages over that described by Goehl and Davison (1):

1. It is applicable, with appropriate choice of internal standard (*i.e.*, similar physiochemical properties to drug) and GC conditions, to most basic drugs and is routinely used in the authors' laboratories for the determination of lidocaine, mepivacaine, etidocaine, bupivacaine, ketamine, and, with small modifications, to base-labile ester-type local anesthetics such as procaine.
2. It has greater sensitivity.
3. It is an internal standard technique and hence is not dependent on volumes transferred, diluted, or injected.
4. No evaporation of solvent is required; therefore, there is no potential for drug loss by volatilization (3, 4).
5. Inclusion of hexamethyldisilazane, with its potential detector contamination problems, is not required.
6. Final solvent may be altered to chloroform for greater polarity or to carbon disulfide (centrifuged at 10,000 rpm for 10 min) for greater sensitivity (*i.e.*, reduced solvent peak size and larger injection volume permitted).
7. This technique may be combined with an alkali flame detector for even greater sensitivity[5].

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[5] L. E. Mather, unpublished observations.

Novel Common Structural Feature among Several Classes of Antimalarial Agents

Keyphrases □ Antimalarial agents—discussion of common structural feature □ Structure-activity relationships—antimalarial agents, common structural feature of several classes discussed

Sir:

A common triangular feature among certain antimalarial cinchona alkaloids, aminoalcohols, and 2-(*p*-chlorophenyl)-2-(4-piperidyl)tetrahydrofuran was recently proposed from this laboratory (1). The components as well as parameters involved in this pharmacophore are interestingly similar to those proposed for α-adrenergic receptor features (2).

In connection with a structural modification study of some 6-aminoquinolines (I) (3–6) and 8-aminoquin-