Table I—Determination of *p*-Hydroxybenzoic Acid in the Presence of Its Alkyl Esters

p-Hydroxybenzoic Acid Taken, μg/ml	Ester Added, μg/ml		ΔA	*p*-Hydroxybenzoic Acid Found, μg/ml
	Propylparaben	Methylparaben		
0.20	0	10.0	0.020	0.22
0.40	0	10.0	0.033	0.39
0.80	0	4.0	0.069	0.86
	0	8.0	0.070	0.88
	0	10.0	0.068	0.85
	0	12.0	0.062	0.77
1.20	0	10.0	0.096	1.22
1.60	0	10.0	0.122	1.56
			0.125	1.60
2.00	0	4.0	0.166	2.14
	0	8.0	0.162	2.09
	0	10.0	0.157	2.02
	4.0	4.0	0.165	2.13
	8.0	0	0.155	2.00
3.20	0	10.0	0.242	3.14
4.00	0	8.0	0.310	4.04
		10.0	0.305	3.97
	4.0	4.0	0.308	4.01
	8.0	0	0.310	4.04
6.00	0	8.0	0.458	5.99
	4.0	4.0	0.460	6.02
10.00	0	8.0	0.762	9.99
	4.0	4.0	0.766	10.0
	8.0	0	0.762	9.99

points between the two species. This result is additional confirmation, as described previously (10), that the esters do not interfere at these points. Moreover, in this example of difference spectroscopy, the interferences were not at low concentration levels but were present at up to 50 times the analate concentration. In addition, as Table I demonstrates, this method is applicable in the presence of mixtures of alkyl paraben esters, giving the total amount of hydrolysis. To determine the relative decomposition of individual esters in mixtures, further direct measurements would be required.

This method is convenient since it avoids the usual preliminary separations and is more rapid than the other methods previously reported. This procedure is especially useful in kinetic studies to monitor the paraben degradation under selected conditions. It possesses the usually sought analytical attributes of simplicity, short analysis time, selectivity, stability of the measurement, linearity, sensitivity, accuracy, and precision.

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Simultaneous Determination of Procainamide and *N*-Acetylprocainamide in Plasma by High-Performance Liquid Chromatography

A. G. BUTTERFIELD ˣ, J. K. COOPER, and K. K. MIDHA

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Abstract □ A sensitive, specific, high-performance liquid chromatographic procedure is described for the simultaneous determination of procainamide and its metabolite, *N*-acetylprocainamide, in plasma. Basic plasma (2.0 ml), containing pheniramine maleate as an internal standard, is partitioned with methylene dichloride. The organic extract is concentrated to between 0.3 and 0.5 ml, and 100-μl aliquots are chromatographed on a microparticulate silica gel column using 0.1% acetic acid–20% 0.1 *M* ammonium acetate in acetonitrile as the mobile phase. With a fixed-wavelength (254-nm) UV detector, both compounds can be quantitated in the 0.1–8.0-μg/ml of plasma range.

Keyphrases □ Procainamide—high-performance liquid chromatographic analysis simultaneously with *N*-acetylprocainamide in plasma □ *N*-Acetylprocainamide—high-performance liquid chromatographic analysis simultaneously with procainamide in plasma □ High-performance liquid chromatography—simultaneous analyses, procainamide and *N*-acetylprocainamide in plasma □ Cardiac depressants—procainamide, high-performance liquid chromatographic analysis simultaneously with *N*-acetylprocainamide in plasma

Several spectrofluorometric and colorimetric procedures were reported (1–5) for the determination of procainamide in plasma; however, these procedures lack specificity because of interference either from *N*-acetylprocainamide, the active metabolite of procainamide (6), or from endogenous materials. Several specific GLC procedures were reported (7–11) for procainamide, but not for *N*-acetylprocainamide, in plasma. One GLC procedure was re-

ported (12) for procainamide and *N*-acetylprocainamide in urine or for *N*-acetylprocainamide in plasma.

High-performance liquid chromatographic (HPLC) procedures were reported for procainamide and lidocaine (13) and for the simultaneous determination of procainamide and *N*-acetylprocainamide in plasma (14). The latter procedure has a reported quantitation as low as 1 μg/ml, adequate sensitivity for clinical work but not for single-dose studies.

None of the available procedures is sufficiently sensitive and/or specific to determine both procainamide and *N*-acetylprocainamide in plasma at the 0.1-μg/ml level. This report describes such a procedure and shows that it can be used to determine drug and metabolite levels following a single oral dose (375 mg) of procainamide hydrochloride.

EXPERIMENTAL

Materials—Procainamide hydrochloride[1] and pheniramine maleate[2] were used as received. *N*-Acetylprocainamide was synthesized from procainamide[2] (15). The proton magnetic resonance spectrum for the product was consistent with the structure of *N*-acetylprocainamide, and a single peak was obtained when the product was examined by HPLC. Solvents and reagents were commercial analytical reagent grade, except for *n*-hexane[3] which was UV grade.

Apparatus—A liquid chromatograph[4] fitted with a valve-loop injector[5] with a 100-μl loop, a fixed-wavelength UV detector[4] (254 nm), and a computing integrator[6] was used. The detector was attenuated to 0.02 absorbance unit full scale (aufs), and the integrator output was attenuated ×16 throughout.

Column—A 250 × 2.16-mm i.d. column packed with 5-μm silica gel[7], using a balanced density slurry technique similar to that described by Majors (16), was used at ambient temperature and a mobile phase flow rate of 60 ml/hr (135 bars).

Mobile Phase—A solution of 0.1% (v/v) acetic acid and 20% (v/v) 0.1 *M* aqueous ammonium acetate in acetonitrile was prepared as required, degassed (refluxed for 5 min), and transferred to the solvent reservoir of the instrument.

Internal Standard—A solution of pheniramine maleate in distilled water (8.9 μg/ml) was used.

Preparation of Standard Curves—Aqueous stock solutions of ammonium hydroxide (0.1 *N*), procainamide hydrochloride (23.1 mg/500 ml), and *N*-acetylprocainamide (20.0 mg/500 ml) were prepared. Standard solutions of procainamide and *N*-acetylprocainamide were prepared by pipetting 80, 60, 40, 20, 10, 5, 2, or 1 ml of both procainamide and *N*-acetylprocainamide stock solutions into each of eight 200-ml volumetric flasks. The resulting solutions were diluted to volume with distilled water.

Extracted standard solutions were prepared by pipetting 2.0 ml of blank plasma, 1.0 ml of procainamide–*N*-acetylprocainamide standard solution, 0.5 ml of 0.1 *N* ammonium hydroxide, 1.0 ml of internal standard, and 15.0 ml of methylene dichloride into a 50-ml screw-capped polypropylene tube[8]. The tube was tightly capped, shaken on a flat-bed shaker[9] at 180 cpm for 10 min, and centrifuged[10] at 3000 rpm for 10 min. A 10-ml aliquot of the organic layer was transferred to a 15-ml conical polypropylene tube[8] and concentrated[11] at 55° under a dry nitrogen stream to 0.3–0.5 ml. The sample was mixed[12] for 10 sec, and duplicate 100-μl aliquots were chromatographed.

Preparation of Calibration Standard Solutions—Two calibration solutions were prepared and chromatographed daily to check the slopes of the standard curves. The solutions were prepared in the same manner as those used for the construction of the standard curves, using procainamide–*N*-acetylprocainamide standard solutions at 0.4 and 4.0 μg/ml (equivalent to 0.2 and 2.0 μg/ml of plasma, respectively).

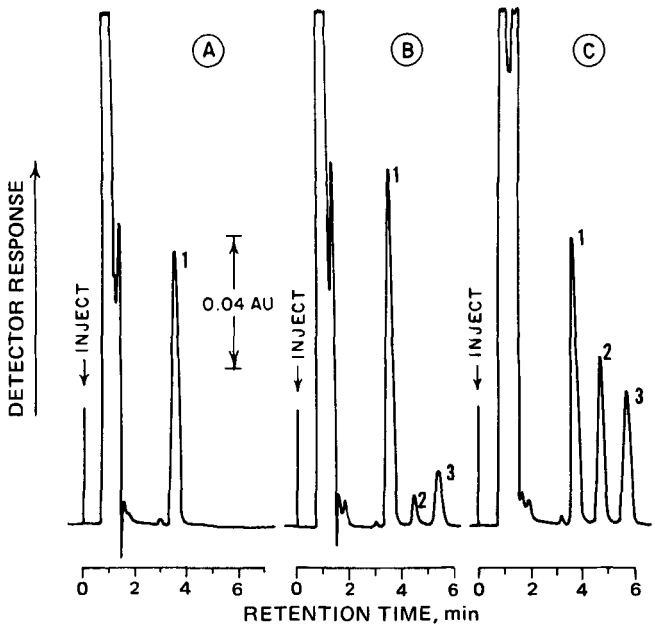

Figure 1—*Chromatograms of an extract of 2 ml of blank plasma containing 6 μg of pheniramine (1) internal standard (A); an extract of 2 ml of spiked plasma containing pheniramine (6 μg), procainamide (2, 0.2 μg/ml) and* N*-acetylprocainamide (3, 0.2 μg/ml) (B); and an extract of a 2-ml plasma sample taken 2 hr postdose (375 mg) estimated to contain 1.3 μg of procainamide/ml and 0.63 μg of* N*-acetylprocainamide/ml (C).*

Determination of Procainamide and *N*-Acetylprocainamide in Plasma—Plasma was treated as described under *Preparation of Standard Curves*, except that 1.0 ml of water was substituted for the procainamide–*N*-acetylprocainamide standard solution. Duplicate 100-μl aliquots of the final solution were chromatographed.

Plasma Level Study—Procainamide hydrochloride[13] (375 mg) was administered orally with 100 ml of water to a 65-kg human male who had fasted overnight. Blood samples, 10 ml, were withdrawn from the cubital vein with heparinized evacuated tubes[14] before dosing and at 10 different times up to 24 hr after dosing. Blood samples were centrifuged, and the plasma was transferred to clean glass tubes before storage at −10°.

Recovery Study—A solution of procainamide hydrochloride (1.155 μg/ml) and *N*-acetylprocainamide (1.0 μg/ml) and a solution of pheniramine maleate (8.9 μg/ml) in methylene dichloride were prepared. Aliquots (1.0 and 4.0 ml) of the procainamide–*N*-acetylprocainamide solution were pipetted into conical polypropylene tubes along with 1.0-ml aliquots of the pheniramine maleate solution. The solutions were mixed[12] briefly and concentrated[11] at 55° under a nitrogen stream to 0.3–0.5 ml. Duplicate 100-μl aliquots of each solution were chromatographed, and the mean sample to internal standard peak area ratios for each drug level were designated as the 100% values.

To determine recovery of procainamide and *N*-acetylprocainamide, 2.0 ml of blank plasma was spiked with 1.0 ml of an aqueous solution of procainamide hydrochloride (1.155 or 4.62 μg/ml) and *N*-acetylprocainamide (1.0 or 4.0 μg/ml). To each solution were added 1.0 ml of distilled water, 0.5 ml of 0.1 *N* ammonium hydroxide, and 15 ml of methylene dichloride. The samples were partitioned as previously described, and 10 ml of the organic layer was transferred to a polypropylene tube containing 1 ml of a methylene dichloride solution of pheniramine maleate (8.9 mg/ml). The resulting solution was concentrated and chromatographed as previously described. The mean sample to internal standard peak area ratios were compared to the 100% values, and the percent recovery was calculated for each level. The recovery of pheniramine maleate was determined similarly, using procainamide as an external standard.

Quantitation—Spiked plasma extracts were chromatographed, and

[1] E. R. Squibb & Sons, Montreal, Canada.
[2] Pfaltz and Bauer, Flushing, N.Y.
[3] Burdick and Jackson Laboratories, Muskegon, Mich.
[4] Model 4100, Varian Aerograph, Palo Alto, Calif.
[5] Model CV-6-UHPa, Valco Instruments Co., Houston, Tex.
[6] Autolab System I, Spectra-Physics, Santa Clara, Calif.
[7] LiChrosorb SI60, British Drug Houses, Toronto, Canada.
[8] Nalge Co., Rochester, N.Y.
[9] Eberbach Crop., Ann Arbor, Mich.
[10] Model HN-S, International Equipment Co., Needham Heights, Mass.
[11] Thermolyne Dri-Bath, Fisher Scientific Co., Ottawa, Canada.
[12] Vortex Genie, Fisher Scientific Co., Ottawa, Canada.
[13] A commercial capsule formulation.
[14] Vacutainers, Becton Dickinson & Co., Mississauga, Ontario, Canada.

Table I—Extractability of Procainamide, *N*-Acetylprocainamide, and Pheniramine from Plasma

Level, μg/ml	Procainamide, % Recovery[a] ± *RSD*	*N*-Acetylprocainamide, % Recovery[a] ± *RSD*	Pheniramine, % Recovery[a] ± *RSD*	*n*
0.5	97.8 ± 4.4	102.8 ± 2.7	—	9
2.0	96.6 ± 0.4	98.9 ± 1.5	—	6
6.0	—	—	98.1 ± 3.3	4

[a] Calculated from recovery values to allow for only 10 ml out of 15 ml of sample being carried through the procedure.

a standard curve was constructed by plotting the ratio of sample to internal standard peak area *versus* the concentration of drug or metabolite (micrograms per milliliter of plasma). Calibration standards were chromatographed periodically to monitor the slope of the standard curve. Unknown plasma samples were analyzed by comparison of peak area ratios to the standard curve.

RESULTS AND DISCUSSION

Procainamide, *N*-acetylprocainamide, and the internal standard (pheniramine) were completely separated and eluted in less than 7 min (Fig. 1B). No interference from endogenous plasma constituents was experienced (Fig. 1A). Mass spectral evidence showed that collected peaks from chromatographed plasma and extracts of spiked blank plasma were identical, indicating that no metabolites of procainamide or *N*-acetylprocainamide interfered.

Stopped-flow injection[4] was used early in the study, but a sample volume in excess of 15–20 μl resulted in excessive peak broadening. Valve-loop injection allowed a 100-μl sample to be chromatographed without affecting peak shape.

A 2.2-mm i.d. column was used to maximize peak height. The peak height obtained with this column was typically about three times that obtained with a 4.6-mm. i.d. column of the same length. Silica gel of 5-μm diameter provided a column that exhibited adequate efficiency and resolution and that can be easily prepared at low cost.

The use of aqueous mobile phases with silica gel columns is often avoided; in certain circumstances, however, this technique has proven to be very useful. Silica gel is somewhat soluble in water, particularly above pH 8, but in practice this solubility has not been a problem. After extended use under aqueous conditions, a silica gel column exhibits some settling of the packed bed (1–2 mm), but this condition is easily remedied by careful addition of moist silica gel to fill the void. The column employed was used over 5 months with only a slight loss of efficiency.

Detector response for *N*-acetylprocainamide (peak area/unit weight) was approximately double that of procainamide, a situation that allows low metabolite levels to be determined despite the longer retention time (5.7 *versus* 4.7 min).

Finding a suitable internal standard for this assay was somewhat difficult. Tetracaine, procaine, methoxyphenamine, and pyrilamine were tried and rejected. Tetracaine exhibited low detector response and presented solubility problems when an adequate quantity was used. Procaine hydrolyzed rapidly under the conditions of the assay. Methoxyphenamine gave a double peak after extraction from certain plasma samples. Pyrilamine also occasionally gave a double peak and, in addition, the shape of the peak varied. This latter observation was explained as being due to the early elution of the compound ($k' = 1.7$). Pheniramine ($k' = 4.3$), the internal standard eventually chosen, eluted just ahead of procainamide. Although occasional broadening of this peak was observed, peak area was unaffected.

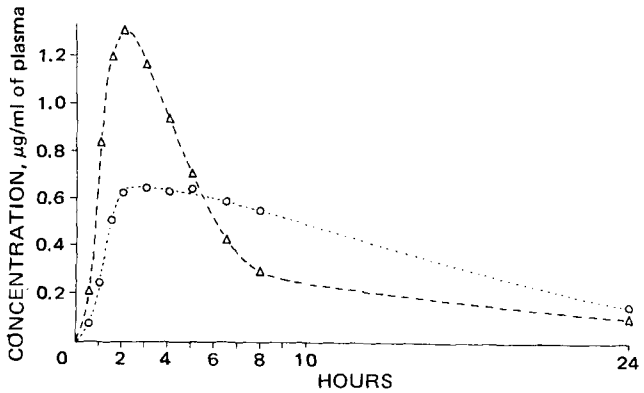

Figure 2—*Plasma profile of procainamide (△) and* N*-acetylprocainamide (○) after a single oral dose (375 mg) of procainamide hydrochloride.*

Aqueous standard solutions of procainamide and *N*-acetylprocainamide exhibited no apparent decomposition after storage for over 6 months at 23°. Solutions of pheniramine maleate appear to be stable for at least 2 weeks at 4°. Extracted procainamide samples gave similar results after storage for 16 hr at 4° as when freshly prepared, but samples generally were analyzed immediately after preparation.

Injection of standard solutions prepared to contain various concentrations of solute provided a linear detector response up to about 6 μg/injection of procainamide hydrochloride, 3.5 μg/injection of *N*-acetylprocainamide, and 4 μg/injection of pheniramine maleate. Standard curves were linear with negligible intercepts over the 0.1–0.8-μg/ml range, with slopes of 0.432 ml/μg for procainamide and 0.832 ml/μg for *N*-acetylprocainamide. Injection of calibration standards over 3 weeks showed that the slopes varied by less than 2% from the values reported.

Nonlinear calibration curves were obtained for both procainamide and *N*-acetylprocainamide if samples were extracted in glass or silanized glass tubes. This phenomenon was attributed to drug adsorption on the glass surface. Carr *et al.* (14) reported similar nonlinearities but overcame the problem by using polypropylene tubes for extraction. Similarly, when polypropylene tubes were used for extraction and concentration in the present study, linear calibration curves were obtained for levels of both drug and metabolite as low as 0.1 μg/ml of plasma.

The extractability of procainamide, *N*-acetylprocainamide, and pheniramine is reported in Table I. The accuracy and precision of the procedure are demonstrated in Table II. Standard solutions prepared over the 0.1–8.0-μg/ml of plasma range were analyzed as described under *Experimental.*

Application of the procedure to the determination of procainamide and *N*-acetylprocainamide in plasma following a single 375-mg oral dose of procainamide hydrochloride is demonstrated in Fig. 2. For plasma from three dosed volunteers, curves with similar shapes were obtained. A first-pass effect has been demonstrated for procainamide (17). This phenomenon was indicated in this study by the presence of *N*-acetylprocainamide approximately 30 min after dosing and by peak plasma levels for both procainamide and *N*-acetylprocainamide about 2 hr after dosing, followed by a slow decline in the metabolite level.

The described HPLC procedure is precise, accurate, and specific for the drug and its metabolite. Furthermore, it is of sufficient sensitivity to determine plasma levels following single doses (375 mg) of the drug

Table II—HPLC Estimation of Procainamide and *N*-Acetylprocainamide Added to Plasma

Concentration, μg/ml	*n*	Procainamide Mean Area Ratio	Procainamide Slope[a]	Procainamide *RSD*, %	*N*-Acetylprocainamide Mean Area Ratio	*N*-Acetylprocainamide Slope[a]	*N*-Acetylprocainamide *RSD*, %
0.1	3	0.043	0.43	5.7	0.081	0.81	5.3
0.2	6	—	—	—	0.169	0.84	4.8
0.5	8	0.225	0.45	3.9	0.417	0.83	1.9
0.8	6	0.352	0.44	1.7	—	—	—
1.0	3	0.455	0.46	0.3	0.834	0.83	1.3
2.0	3	0.902	0.46	1.2	1.670	0.84	1.3
8.0	3	3.460	0.43	0.9	6.53	0.82	1.4
		Mean	0.445	3.1		0.829	1.6

[a] Slope = mean area ratio/concentration.

and should be suitable for single- or multiple-dose pharmacokinetic or bioavailability studies.

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Noninvasive Polarographic Measurement of Drug Dissolution

M. R. HACKMAN ˣ **and M. A. BROOKS**

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Abstract □ Polarographic analysis was applied successfully to dissolution studies and content uniformity assessment of both capsules and tablets, using a dropping mercury electrode with the modified Levy beaker method. The described noninvasive technique places the polarographic sensor probe directly into the dissolution flask and thus simplifies dissolution measurement by eliminating transfer lines and pumps typically required with the invasive (sampling) mode of analysis. A continuous sampling flowcell with polarographic detection was also evaluated for invasive measurements. Continuous dissolution profiles and content uniformity were determined for chlordiazepoxide, trimethoprim, ornidazole, and isoniazid, using the invasive and noninvasive sampling modes. Results obtained for these drugs showed excellent precision with both sampling techniques. In addition, excellent correlation to UV spectrophotometric data was obtained.

Keyphrases □ Polarography, noninvasive—applied to drug dissolution and content uniformity assessment of various capsules and tablets □ Dissolution, drug—noninvasive polarographic study of various capsules and tablets □ Content uniformity—noninvasive polarographic assessment of various capsules and tablets

The dissolution rate of a drug is determined by measuring the amount dissolved per unit of time. These measurements are obtained conventionally by two invasive sampling techniques: (*a*) discrete sampling of the medium in the dissolution flask, followed by spectrophotometric analysis; and (*b*) continuous sampling and measurement by pumping of the dissolution medium through a UV spectrophotometer. A proposed means of obtaining dissolution data is *via* direct or noninvasive measurement by placement of an analyzing sensor directly into the dissolution flask. Spectrophotometric measurement using the noninvasive technique is not possible because of the lack of a spectrophotometric probe. Other limitations of a spectrophotometric method include disturbances caused by the stirring action, the presence of excipients, and a limited linear dynamic range.

Voltammetric analysis, which has been well documented for assays of drugs in dosage forms (1, 2) and biological fluids (3, 4), can be applied to both invasive and noninvasive dissolution measurements. The only prerequisite is that the drug undergo voltammetric reduction or oxidation in the dissolution medium. Voltammetric analysis is ideally suited for drug dissolution measurements since the technique has a wide linear dynamic range. In addition, these assays are specific for the compound of interest in the presence of excipients. The method also permits the analysis of content uniformity on the same sample after dissolution. Feher *et al.* (5) reported the use of voltammetry for the continuous invasive measurement of the dissolution of aminopyrine and promethazine by oxidation using a silicone rubber-based graphite electrode. Gaglia *et al.* (6) recently reported the noninvasive voltammetric analysis of the dissolution of nitroglycerin tablets by reduction of the nitro group at a rotating platinum electrode.

The use of a polarographic sensor, the dropping mercury electrode (DME), for drug dissolution measurement is being described for the first time. The dropping mercury electrode, when used either in a flowcell (continuous invasive measurement) or directly in the dissolution flask (noninvasive measurement), has the distinct advantage over other voltammetric sensors of presenting a constantly renewable surface for analysis. Therefore, it is not subject to a buildup of interferences during dissolution.

Polarography was used in this study to measure the dissolution rate of four drugs, chlordiazepoxide (I), or-