Derivatives of 4-Trichloromethylbenzoyl Chloride (XI)—*4-Trichloromethylbenzanilide* (*VI*d)—A solution of XI and aniline in tetrahydrofuran gave VI*d*; IR (mineral oil): 3310 and 1650 cm^{-1}.

4'-Nitro-4-trichloromethylbenzanilide (*VI*e)—A solution of XI, 4-nitroaniline, and triethylamine in acetonitrile gave VI*e*; IR (mineral oil): 3390 and 1670 cm^{-1}.

S-(Phenyl)-4-trichloromethyl Thiolbenzoate (*VI*f)—A solution of XI, thiophenol, and triethylamine in tetrahydrofuran gave VI*f*; IR (mineral oil): 1660 cm^{-1}.

S-(4-Acetamidophenyl)-4-trichloromethyl Thiolbenzoate (*VI*g)—A solution of XI, 4-acetamidothiophenol, and triethylamine in tetrahydrofuran gave VI*g*; IR (mineral oil): 3250 and 1660 cm^{-1}.

α-Disulfones and Thiolsulfonates—*Bis(4-acetylaminophenyl Sulfone)* (*VIII*a)—This was prepared (30) from 4-acetamidophenyl sulfinic acid and potassium permanganate, mp 245° [lit. (30) mp 245–250° dec.].

Bis(4-aminophenyl Sulfone) (*VIII*b)—Acid hydrolysis of VIIIa in hydrochloric acid, methanol, and *N*-methyl-2-pyrrolidone at 100° for 2 hr gave VII*b*. Compound VIII*b* was recrystallized from a mixture of *N*-methyl-2-pyrrolidone and water, mp 215° dec. (31); IR (mineral oil): 3490, 3400, 1320, and 1125 cm^{-1}.

Anal.—Calc. for $C_{12}H_{12}N_2O_4S_2$; C, 46.14; H, 3.88; N, 8.97; S, 20.53. Found: C, 48.87; H, 4.10; N, 8.89; S, 20.39.

4'-Acetamidophenyl-4-acetamidobenzene Thiolsulfonate (*IX*a)—Compound I*a* (6.35 g, 15 mmoles) was suspended in 55 ml of acetic acid, and 30% hydrogen peroxide (8.55 g, 75 mmoles) was added during 30 min. The temperature of the reaction mixture was kept below 35° with occasional ice cooling during the addition of hydrogen peroxide. Stirring was continued for 37 hr. The suspension was poured into 450 ml of water and the undissolved material was filtered, and washed with water giving 4.34 g (81.5%) of IX*a*, mp 219–221° dec. Recrystallization from a mixture of *N,N*-dimethylformamide and water gave 3.22 g (59%) of IX*a*, mp 223–224° dec. [lit. (30) mp 236–237° dec.].

4'-Aminophenyl-4-aminobenzene Thiolsulfonate (*IX*b)—This compound was prepared by acid hydrolysis of IX*a* in hydrochloric acid and methanol, mp 185–186° dec. [lit. (30) mp 183°].

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GLC Analysis of Trifluoperazine in Human Plasma

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Received March 6, 1981, from the **Illinois State Psychiatric Institute, Chicago, IL 60612*, and the *‡National Psychopharmacology Laboratory, Knoxville, TN 37923.* Accepted for publication May 21, 1981.

Abstract □ This report describes a sensitive gas chromatographic procedure for the measurement of trifluoperazine in human plasma. Trifluoperazine was extracted into heptane-2-propanol by a two-step procedure and analyzed directly without derivatization. Prochlorperazine was employed as an internal standard because its structural and extraction characteristics were similar to trifluoperazine. The use of a nitrogen detection system reduced the number of interfering peaks. The within-day coefficient of variation in the method, over a 0.2–20-ng/ml concentration range was 9.4%.

Keyphrases □ Trifluoperazine—gas chromatographic measurement in human plasma □ Gas chromatography—measurement of trifluoperazine in human plasma □ Tranquilizers—trifluoperazine, gas chromatographic measurement in human plasma

The relationship between plasma concentrations of various psychoactive drugs and their clinical effects was recently discussed (1, 2). It was shown that drug concentrations can vary widely among patients receiving identical doses (3–6). Based on such interindividual variations in plasma levels of psychoactive drugs, it was suggested that

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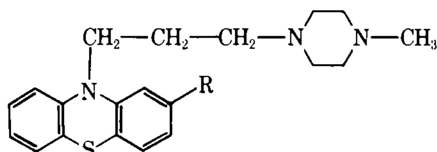

an effective treatment regimen for the individual patient may be approached by monitoring the blood levels of the drug and relating them to clinical outcome. Therefore, specific and sensitive methods for measuring neuroleptic drug levels in schizophrenic patients (7, 8) are needed.

Trifluoperazine (I), a phenothiazine neuroleptic, is commonly used for the treatment of schizophrenia. Although a TLC method for the measurement of trifluoperazine and its metabolites in rat tissues was reported (9), the method was not sensitive enough to measure the low therapeutic levels in humans. The present report describes a specific and sensitive method for measuring trifluoperazine in biological fluids. Prochlorperazine (II) was the internal standard. The method was applied to measure plasma trifluoperazine concentrations in schizophrenic patients treated with the drug.

EXPERIMENTAL

Materials—Trifluoperazine hydrochloride[1] and prochlorperazine maleate[1] were used. Heptane[2] and 2-propanol[2] were glass distilled. All other reagents were analytical grade.

The gas chromatograph[3] was equipped with a nitrogen–phosphorus detector; 3% OV-101 on 80–100-mesh support[4] was used as packing material. The highest purity[5] air, helium, and hydrogen available were used.

Procedures—Blood was drawn into tubes[6] containing ethylenediaminetetraacetate (1 mg/ml of blood) from patients receiving trifluoperazine. Rubber[6] stoppers were avoided since it was reported (10) that contact with the stopper may alter the distribution of drugs between plasma and red blood cells. The plasma and red blood cells were separated by centrifugation and stored at −16° until analysis. For determining recoveries and preparing standard curves, outdated plasma was used since there were no differences in recoveries with fresh and outdated blood.

Extraction from Plasma—Five-milliliter plasma samples, (unknown, drug-free, and plasma standards containing known amounts of the drug) were transferred to 15-ml test tubes, and prochlorperazine (as the internal standard) was added to unknown samples and plasma standards. To each tube, 1.0 ml of 2 *N* NaOH was added, and the mixture extracted with 5 ml of heptane–2-propanol (9:1, v/v). After shaking for 20 min, the tubes were centrifuged to separate the organic and aqueous layers.

The upper organic layer was transferred to another 15-ml tube containing 1 ml of 0.1 *N* HCl. The mixture was shaken for 15 min, and the organic layer was discarded by aspiration after centrifugation. The acid layer was transferred to a 5-ml centrifuge tube containing 0.1 ml of 5 *N* NaOH, and the mixture was extracted with 0.3 ml of heptane–2-propanol after shaking for 5 min and centrifuging as described. The organic layer (3–5 μl) was then injected into the gas chromatograph.

Chromatographic Conditions—The instrument was set according to the instruction manual provided by the manufacturer, except that the off-set current applied to the detector was increased until an optimum signal-to-noise ratio was obtained to maximize sensitivity. Generally, the detector voltage was set to give a 20% deflection of the recorder chart at the range setting of 1 and an attenuation of 32 at a 190° oven temperature.

When a 0.9 m glass column (2-mm i.d.), packed with 3% OV-101 was used, the chromatographic conditions were as follows: isothermal column temperature, 250°; injection port temperature, 300°; detector temperature, 300°; carrier gas (helium) flow, 30 ml/min; air flow, 50 ml/min; hydrogen flow, 3 ml/min; range, 1; and attenuation, 2–32.

Calculations—A standard curve was prepared with every analysis by plotting the ratio of peak heights for trifluoperazine and prochlorperazine against various concentrations of trifluoperazine added to the drug-free plasma samples. The inverse of the slope of the line thus obtained was used to calculate the trifluoperazine concentration in unknown samples.

[1] Smith Kline and French Laboratories, Philadelphia, Pa.
[2] Burdick & Jackson Laboratories, Muskegon, Mich.
[3] Model 5730-A, Hewlett-Packard, Avondale, Pa.
[4] Supelco, Bellefonte, Pa.
[5] Liquid Carbonic, LaGrange, Ill.
[6] Vacutainer, Becton-Dickinson, Rutherford, N.J.

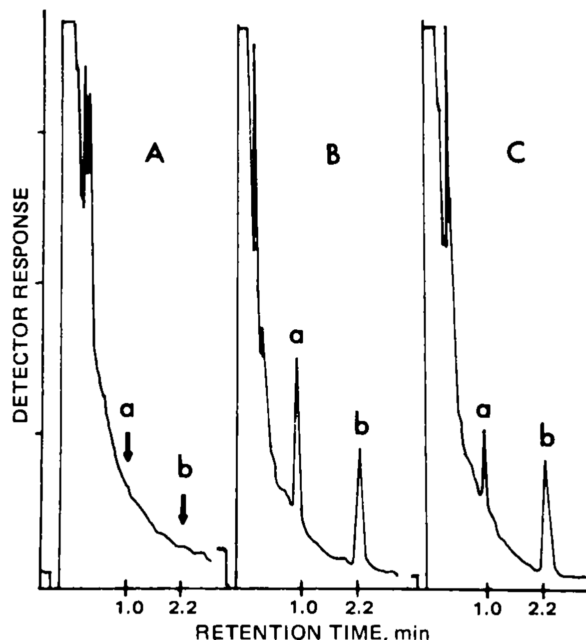

Figure 1—*Typical chromatogram of drug-free plasma carried through the procedure (A), drug-free plasma to which trifluoperazine (a) and prochlorperazine (b) were added (B), and plasma from a patient receiving trifluoperazine (C). Prochlorperazine was added as an internal standard.*

RESULTS

Figure 1 shows a typical chromatogram obtained for the analysis of trifluoperazine with the internal standard, using a 0.9 m column packed with 3% OV-101 at 250°. There were no interfering peaks at the retention times for trifluoperazine and prochlorperazine (Fig 1A). The peaks for trifluoperazine and prochlorperazine were symmetrical, and relationship was linear between the peak height and concentration of each drug injected into the chromatograph. There was also a linear relationship when the ratios of the peak height of trifluoperazine to the peak height of prochlorperazine were plotted against the various concentrations of trifluoperazine ($y = 0.055 + 0.126x$, $r = 0.996$).

Recovery of Extraction Procedure—The recoveries of trifluoperazine and prochlorperazine were determined by adding varying concentrations of the standard solution to drug-free plasma. These samples were then extracted and analyzed by the described procedure. The recoveries were calculated by comparing the extracted samples with the standard curves obtained by directly injecting the methanolic solutions of the drugs without extraction.

Trifluoperazine recovery from plasma averaged 79% and was constant over a wide concentration range (0.2–100 ng/ml). The average recovery of prochlorperazine from plasma was 72%.

Table I—Accuracy of Trifluoperazine Determination in Human Plasma [a]

Added, ng/ml	Determined, ng/ml	*SD*	Number of Determinations
20.0	20.77	1.1	9
2.0	2.17	0.13	10
0.2	0.23	0.02	10
0.1	0.16	0.07	6

[a] Different concentrations of trifluoperazine were added to drug-free plasma, and samples were then analyzed by the described procedure.

Table II—Reproducibility of Trifluoperazine Determination over Time [a]

Amount Added, ng/ml	Amount Determined over Time, ng/ml						Average ± SD
	1 Day	3 Days	4 Days	6 Days	8 Days	33 Days	
1.0	0.93	1.03	0.83	0.83	0.82	1.1	0.92 ± 0.11
2.0	1.9	1.70	1.70	1.60	2.0	2.4	1.88 ± 0.27
4.0	4.3	3.7	3.6	4.4	3.3	3.8	3.85 ± 0.39
8.0	8.0	7.7	7.6	7.5	7.7	7.8	7.72 ± 0.16

[a] Different concentration of trifluoperazine were added to drug-free plasma and kept frozen in aliquots. Each aliquot was thawed on the day of analysis.

Accuracy and Reproducibility—The accuracy of the method was determined by adding different concentrations of trifluoperazine and analyzing six to 10 samples for each concentration according to the described procedure. These results are summarized in Table I. The within-day coefficient of variation over the concentration range of 0.2–20 ng/ml plasma was calculated as 6.7%.

To determine the day-to-day reproducibility, four different trifluoperazine concentrations were added to drug-free plasma and the samples were analyzed over the next several days. The average day-to-day coefficient of variation over the 1.0–8.0-ng/ml concentration range was calculated as 9.4%. These results (Table II) also indicate that the trifluoperazine in plasma samples was stable for at least 1 month when kept frozen.

Specificity and Sensitivity—Evidence for the specificity of the method was provided by characteristic retention times of trifluoperazine and prochlorperazine and the lack of interfering peaks in drug-free plasma when the samples were analyzed by the described procedure. Ten commonly used psychoactive drugs and three metabolites of trifluoperazine were also screened for interference in the assay by directly injecting their methanolic solutions under the described chromatographic conditions. The retention times of these drugs relative to trifluoperazine were as follows: butaperazine, 5.92; clomipramine, 0.50; desipramine, 0.33; desmethyltrifluoperazine, 0.83; diazepam, 0.58; fluphenazine, 2.50; haloperidol, 2.00; 7-hydroxytrifluoperazine, 2.42; imipramine, 0.25; mesoridazine, 5.83; piperacetazine, 10.00; prochlorperazine, 2.18; thioridazine, 2.75; 2-trifluomethylphenothiazine, 0.17; and trifluoperazine, 1.00. None of the drugs tested interfered with the assay of trifluoperazine or prochlorperazine.

Although 0.1 ng of trifluoperazine/ml could be measured by the described procedure, the coefficient of variation was too large (43.8%, Table I) for quantitative purposes. Hence, the actual sensitivity of the method to quantitate trifluoperazine in plasma was 0.2 ng/ml (coefficient of variation of 8.7%, Table I) when 5 ml of plasma sample was used.

Trifluoperazine Levels in Clinical Samples—The described method was used for measuring plasma concentrations of trifluoperazine in patients who received therapeutic doses for schizophrenia. The steady-state plasma levels in 21 patients receiving different doses of trifluoperazine are shown in Fig. 2. Although there were large interindividual differences in steady-state plasma concentrations in patients receiving identical doses of trifluoperazine, there was good correlation between drug concentation in plasma and dose administered ($r = 0.93$). However, some patients received other medication along with trifluoperazine. These data are given to show the applicability of the method in patients treated with trifluoperazine.

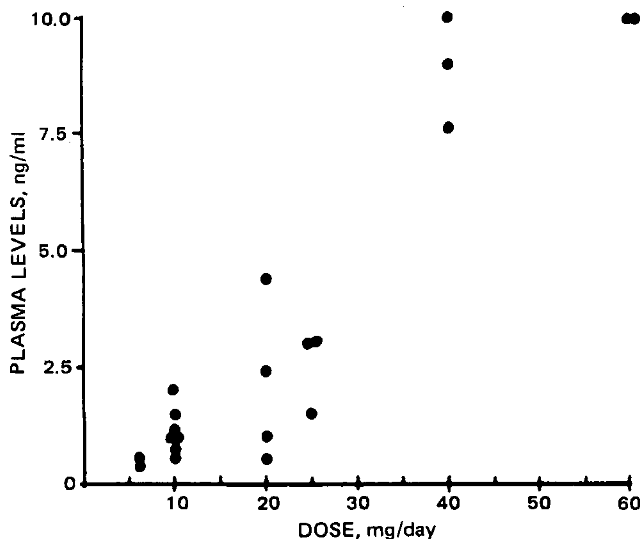

Figure 2—*Trifluoperazine concentrations in plasma from patients receiving different doses of the drug.*

DISCUSSION

The described procedure is sensitive enough to measure low therapeutic levels, is specific, and is reproducible for trifluoperazine. Detector response for trifluoperazine and prochlorperazine was linear over a wide concentration range, and retention times were similar.

In one experiment where trifluoperazine was added to drug-free plasma without any preservative and the sample was analyzed over the next 33 days, the sample was stable when kept frozen. However, during more than 1 year of analysis of plasma samples from patients, samples were found to be more prone to losses without any preservative.

Although there are no systematic studies on the stabilities of neuroleptics, it was reported (11) that amitriptyline hydrochloride in aqueous solutions is broken down by heavy metal contaminants. If this is also the case for neuroleptics, all the glassware should be acid washed and rinsed thoroughly with distilled water. This procedure minimizes occasional problems with the assay. Furthermore, 0.5 mg of sodium metabisulfite or ascorbic acid/ml of plasma should be added to samples to avoid loss by oxidation. In addition, all standard solutions should be stored in dark bottles or covered with aluminum foil. Although trifluoperazine standard solutions were stable for up to 3 weeks when kept at −16° in the dark, the prochlorperazine standard was stable for only 1 week.

The steady-state plasma concentrations of trifluoperazine showed interindividual variability in patients receiving identical doses. Such interindividual variabilities are characteristic of most of the drugs and represent the differences in absorption, distribution, metabolism, and excretion due to genetic, physiological, and environmental differences. Steady-state plasma concentrations were similar to those reported for another high potency neuroleptic, fluphenazine (12, 13), but were much lower than with chlorpromazine (14) or butaperazine (7). In one patient, the pharmacokinetics of trifluoperazine after a single dose were also studied using the described procedure. Highest concentrations were obtained in 4 hr after oral drug administration and then decreased over the next 24 hr.

Although radioreceptor assay was recently introduced (15) for measuring total neuroleptic concentrations, this assay did not differentiate between the parent compound and active metabolites. Furthermore, the lower limit of sensitivity of the radioreceptor assay for trifluoperazine is 2.2 ng/ml (15) because $<200\ \mu l$ of plasma or serum must be used in the assay system; at higher protein concentrations, the nonspecific inhibition in the binding system becomes significant. On the other hand, the lower limit of sensitivity of the described method is 0.2 ng/ml, because 5 ml of the plasma can be used for extraction.

GLC with nitrogen detection is becoming increasingly popular for measuring low drug levels in therapeutic conditions. The nitrogen detector is 10–100-fold more sensitive than the conventional flame-ionization detector and is as sensitive as the electron-capture detector for nitrogen-containing compounds. The selectivity of the nitrogen detector reduces the number of interfering peaks and decreases the time for sample analysis. The method described here for trifluoperazine determination does not require any derivatization and takes only 3 min for each sample analysis after extraction.

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Contribution of Lungs to Total Body Clearance: Linear and Nonlinear Effects

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Received October 29, 1980, from the *Biomedical Engineering and Instrumentation Branch, Division of Research Services, National Institutes of Health, Bethesda, MD 20205.* Accepted for publication May 13, 1981.

Abstract □ The contribution of the lungs to the total body clearance of drugs is examined in a framework that emphasizes their anatomical position. For intravenous administration, the lung is the only organ other than blood that can account for a total body clearance in excess of the cardiac output. Systemic arterial drug concentration and tissue drug exposure are inversely proportional to total body clearance. Although the role of the lung has been overshadowed by that of the liver, several examples are presented to demonstrate that a relatively small amount of pulmonary activity can produce a large reduction in systemic arterial drug concentration. For oral administration, first-pass elimination by the liver and lungs in series results in a synergistic increase in total body clearance. Nonlinear effects caused by saturation of elimination pathways are also examined. Increased emphasis on experimental investigation of the pulmonary contribution is warranted, especially for drugs with high apparent clearance.

Keyphrases □ Lungs—role in total body clearance, linear and nonlinear effects □ Pharmacokinetics—role of lungs in total body clearance, linear and nonlinear effects □ Pulmonary metabolism—role in total body clearance, linear and nonlinear effects

Application of the techniques used to study hepatic drug metabolism to the lung has led to a growing literature on pulmonary metabolism. Although smaller in weight than the liver (600 *versus* 1500 g for humans), the processing of the entire cardiac output (*versus* 25% for the liver) places the lungs in a unique position for drug metabolism.

This report describes the contribution of the lungs to drug metabolism, including interaction with other drug-eliminating organs. Both saturating and nonsaturating conditions were examined.

BACKGROUND

Of the three types of clearance mechanisms (metabolism, excretion, and irreversible binding), this report concentrates on metabolic clearance. Transport, including excretion, of volatile substances is a primary function of the lungs; however, this topic was previously detailed (1). Uptake and/or binding of substances by the lung was documented by Junod (2). He suggested that the lungs can function as a capacitor that dampens out large variations in plasma concentration by rapid uptake and slow release processes. While such a role could have major importance for the pharmacodynamics of drug effect, reversible uptake or binding makes no net contribution to apparent clearance. Only irreversible binding decreases the total amount of drug delivered to the systemic circulation.

The demonstration of drug metabolism at the cellular (3) and subcellular level (4, 5) was a first step in the stimulation of more interest in pulmonary metabolism. Although some metabolic activity was shown in subcellular preparations from the lungs, recent work (6) raised the possibility that pulmonary activity has been substantially underestimated due to undetermined methodological factors. The isolated perfused lung preparation was shown to possess 10 times more drug clearance capability than was projected on the basis of experiments using subcellular preparations.

The isolated perfused lung has had a major role in demonstrating the importance of pulmonary metabolism. An earlier report (7) detailed the capability of this preparation to extract certain endogenous substances, especially the prostaglandins (8), serotonin (9), and other hormones. Metabolic clearance by the isolated perfused lung has now been demonstrated for many exogenous substances including drugs such as mescaline (10), isoproterenol hydrochloride (11), and the tetrahydrocannabinols (12) and chemicals such as *N*-methylaniline (13), aldrin (14), and trichloroethylene (15).

Direct comparisons of lung and liver elimination capacity were made by Roth and coworkers for three substances. In all cases, the effect of blood flow limitation increased the relative role of the lungs *versus* the liver when organ clearance was compared with organ enzyme capacity. Using literature values (16, 17) for benzpyrene in rats with induced enzymes, Roth and Wiersma (18) calculated nearly equal organ clearances for the liver and lungs, despite the fact that the liver contained 64 times more total enzyme capacity than the lungs. Similar calculations were reported (10) for data on mescaline metabolism in homogenates of rabbit lungs and liver. Approximately equal organ clearances were predicted, despite five times more enzyme capacity in the liver. For serotonin, Wiersma and Roth (6) found 17 times as much activity in the liver as in the lungs and predicted five times more clearance in the liver than the lungs. Their predictions for the perfused liver agreed well with their experimental results, but they underpredicted perfused lung clearance by a factor of 10. This discrepancy may be attributed to either suboptimal lung homogenate experiments or strong binding of serotonin by lung tissue.

The demonstration of *in vivo* pulmonary metabolism fully established the key role of the lungs in the overall process of drug elimination from the body. Two studies (19, 20) demonstrated a pulmonary extraction for phenol of ~60% in the rat by comparing the area under the plasma concentration–time curve following intravenous and intra-aortic administration.

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