Table I—Comparison of Dithizone Colorimetric and HPLC Methods for Thimerosal Determination

Sample	Thimerosal, μg/ml	
	Colorimetric	HPLC
1	11.5	11.9
2	11.5	11.7
3	11.8	12.3

calcium chloride solution). The amount of calcium chloride added to the sample solution depended on the actual amount of edetate disodium present. Since the complexation of edetate disodium with metal ions is pH dependent, one must adjust the sample solution pH to between 6.8 and 7.4 to obtain the best results.

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Sex Differences in Drug Evaluations

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Abstract □ Twenty normal, nonobese subjects (10 male and 10 female) were administered a battery of seven psychomotor tests as well as affect checklists and physiological measurements on 6 alternate days. Subjects performed the entire battery predrug and at 45, 90, and 135 min postdrug. Fenfluramine, dextroamphetamine, two combined doses of the drugs, and a placebo were given in a double-blind, repeated measures design. Findings revealed significant sex-based differences in initial performance on five of the seven psychomotor tasks and in two physiological measures, with males performing at higher levels than females. Additionally, sex differences in postdrug changes were found in three psychomotor and two physiological measures, with females evidencing greater change scores than males.

Keyphrases □ Fenfluramine—alone and combined with dextroamphetamine, sex-based differences in psychomotor and physiological effects, humans □ Dextroamphetamine—alone and combined with fenfluramine, sex-based differences in psychomotor and physiological effects, humans □ Psychomotor effects—fenfluramine and dextroamphetamine, alone and in combination, sex-based differences, humans □ Physiological effects—fenfluramine and dextroamphetamine, alone and in combination, sex-based differences, humans □ Sex-based differences—fenfluramine and dextroamphetamine, alone and in combination, psychomotor and physiological effects, humans

Fenfluramine is an anorexic agent structurally similar to dextroamphetamine; however, it does not produce central nervous system (CNS) activation with respect to measures of sleep (1) or psychomotor performance (2). The mood elevation, euphoria, and lift produced by dextroamphetamine are well documented (3–5); fenfluramine, however, appears to have sedative properties (2, 4, 6). There is some evidence that fenfluramine may block the CNS stimulant effects of dextroamphetamine (7).

As with most psychopharmacological investigations, sex-based differences in drug reactivity were not explored in the studies cited (8). A chance assignment of subjects in a study to be reported elsewhere provided a comparison of pre- and postdrug performance and mood differences between the sexes given identical treatments. Based upon a preliminary analysis, it was hypothesized that males would have higher levels of performance on psychomotor tests than would females and that sex differences would occur in the pattern of drug reactivity.

EXPERIMENTAL

Twenty subjects (10 male and 10 female, age range of 21–30, $\bar{X}$ = 23.7) were recruited by newspaper advertisements and screened by psychiatric interview and psychological test (16 PF) (9). Informed consent was obtained and subjects were paid for their participation. Subjects were asked to abstain from all medication and alcohol and to maintain normal diet and sleeping habits during the 2-week testing period.

Subjects were tested at the same time of day (11:30 am–5:00 pm) on 6 alternate days. The 1st day was primarily for practice and familiarization with the tests, and this day's data were subsequently discarded. On each of the remaining 5 test days, the subject performed the entire test battery of psychomotor, perceptual, physiological, and affect evaluations prior to receiving medication and at 45, 90, and 135 min postmedication (exceptions noted in test descriptions).

Five treatments were used: (*a*) placebo (lactose), (*b*) fenfluramine alone (60 mg), (*c*) dextroamphetamine alone (10 mg), (*d*) a low combination (60 mg of fenfluramine plus 10 mg of dextroamphetamine), and (*e*) a high combination (90 mg of fenfluramine plus 10 mg of dextroamphetamine).

Each of the five conditions appeared equally on each test day, and subjects were randomly assigned to a treatment sequence upon acceptance. Postdrug measures were compared against the predrug baseline for each subject on each test day to minimize practice and potential day-of-week effects. Both the subject and experimenter were unaware of the contents of the identically appearing capsules. In the five treatment groups representing orders of administration of placebo and four drug conditions, males and females appeared in the ratios of 1:1, 0:1, 3:1, and 1:3. This approach provided the opportunity for an evaluation of study results with sex as a main factor.

The test battery included various psychomotor tasks, several physiological measures, and self-report mood evaluative forms. Psychomotor tests have been shown to be sensitive to various drug effects (8, 10) and were used previously in this laboratory (2).

Physiological Measures—Pulse rate, oral temperature, blood pressure, and salivary output were taken daily prior to drug administration and at 200 min postdrug; pupil size was measured predrug and at 45, 90, and 135 min postdrug. Additionally, the Lorr outpatient mood scale

Table I—Means, Standard Deviations, and t and p Data for Males and Females in Predrug Performance Level

Test		Female	Male	1 t 1	p
Tapping rate	Mean	305.06	400.42	3.60	0.005
	SD	22.01	14.73		
Card sorting	Mean	98.62	108.28	2.05	0.05
	SD	3.69	2.94		
Reaction time	Mean	0.81	0.57	4.59	0.0005
	SD	0.05	0.02		
Steadiness	Mean	11.28	5.23	2.93	0.005
	SD	1.96	0.64		
Handwriting	Mean	71.41	97.85	1.84	0.05
	SD	11.17	8.57		
Systolic blood pressure	Mean	104	111	4.47	0.0005
	SD	1.47	0.83		
Temperature	Mean	98.08	97.72	1.91	0.05
	SD	0.14	0.13		

(LOMS) and an adjective checklist were completed 160 min postmedication.

Psychomotor Performance Measures—*Tapping Rate*—The subject was instructed to tap as rapidly as possible with the forefinger of the preferred hand on a standard telegraph key for 1 min. The score was the number of taps.

Cross-Out Rate—The subject was required to make a slash through each X on a 21.6 × 28-cm sheet of paper with X's and O's in random order typed in continuous double-spaced rows. The score was the number of X's crossed out.

Reaction Time—The subject was instructed to react as quickly as possible to a signal light mounted on the response key 30.5 cm from the subject's hand by pressing the key at the appearance of the light. Twenty-five trials with randomized intertrial intervals were presented during 2 min. The score was the average reaction time in milliseconds.

Steadiness—The subject was given a pistol handle connected to a light metal rod 0.63 cm in diameter and 91.4 cm long, the end of which was placed in the center of a hole 1.2 cm in diameter. Contact between the rod and the hole produced an audible tone and activated a timer. The task was to hold the rod, with the elbow locked, in the center of the hole without touching the side for 60 sec. The score was time in milliseconds that the rod touched the side.

Number Path—The subject was instructed to connect the numbers one through 30 interspersed over a paper. The score was the number reached after 30 sec (11).

Card Sorting—The subject was required to sort four decks of playing cards into suits by placing them face down into the four divisions of a sorting bin. The score was the number of cards sorted.

Handwriting—The subject was asked to copy a standard paragraph on a piece of paper 21.6 × 28 cm. The score was the area in centimeters squared covered by the handwriting (12).

RESULTS

Male and female groups did not differ significantly on height–weight ratio, age, or 16 PF profiles.

Data were gathered across subjects and days with each subject serving as his or her own control. An analysis was undertaken to determine differences between sexes with regard to the baseline level of performance of the tests and differences in drug-modified performance.

Five of seven psychomotor tests, three physiological measures, and four LOMS factors revealed one or the other type of sex-based difference.

Predrug Sex Differences—Differences in the initial level of daily task performance between men and women were assessed by a t for correlated means (Table I). Significant pretreatment sex differences were found for five of the seven psychomotor tasks. In each case, the magnitude of male performance exceeded that of females. Males tapped more times in a minute, sorted more cards, reacted more quickly to a stimulus, were steadier, and covered a larger area with their handwriting than did females. Men also displayed a lower temperature and a higher systolic blood pressure.

Since the Lorr outpatient mood scale (LOMS) was given only once, 160 min postmedication, those ratings reflect a combination of drug-induced and predrug mood states. Males rated themselves significantly higher in total affect, energy level, "anger," and "cheerfulness" than did females.

Sex Differences in Drug Reactivity—Difference scores were obtained by subtracting each subject's predrug score from the scores obtained at 45, 90, and 135 min postdrug. A three-way analysis of variance (repeated measures) was employed on these difference scores, followed by t tests where significance was found. Sex appeared as a significant main factor in three psychomotor tasks and two physiological measures. In each case, females had greater change scores than did males (Table II).

Table II—Postdrug Change Scores for Males and Females

Test		Female	Male	F
Tapping rate	Mean	13.73	5.99	5.36[a]
	SD	3.23	1.89	
Card sorting	Mean	4.48	1.73	8.87[b]
	SD	1.04	1.18	
Steadiness	Mean	−1.91	−0.78	13.68[b]
	SD	0.39	0.29	
Systolic blood pressure	Mean	4	0	5.06[a]
	SD	1.92	1.15	
Pulse	Mean	0.28	−4.96	7.60[b]
	SD	1.32	1.94	

[a] Significant at 0.05. [b] Significant at 0.01.

Females had a significantly greater increase in card sorting, tapping rate, and steadiness after drugs than males had. Additionally, females showed greater changes in the physiological measures of systolic blood pressure and pulse rate. Although the systolic blood pressure of *both* males and females increased from pre- to postdrug, females increased significantly more than males. The differences in pulse rate change between the two sexes also achieved significance; while the pulse rate of women subjects increased after drugs, that of male subjects decreased.

DISCUSSION

These results suggest that there are significant sex-based differences in the initial performance of certain psychomotor tasks. Five of the seven psychomotor tasks used revealed significantly higher initial levels of test performance for males than for females. The rate of change in performance, *i.e.*, drug reactivity, following drugs may be partially determined by the sex of the subject. In this study, females had a greater change after drugs than did males.

The observed differences in certain physiological measures (pulse, blood pressure, and temperature) both pre- and postdrug may point to metabolic differences between males and females. Although there was no significant difference between the ratio of height to weight between males and females, the females were on the average 9.07 kg lighter than the males. This factor, along with probable differences in the proportion of fat and muscle, may contribute both to predrug differences as well as differences in reactivity. Further study of male–female reactivity to drugs and situational changes is definitely indicated.

The data from the Lorr outpatient mood scale, which showed that males rated themselves higher in affect, also need to be explored further. Since the design of the study had subjects completing the scale only after medication, it could not be determined if this sex difference was due to drug reactions, procedural factors, or basic difference between male and female awareness of and/or reporting of different feelings.

In the performance of the simple psychomotor tasks, the males excelled initially while the females showed greater postdrug changes. The effect of learning on the postdrug performance must be considered. Women have been shown to excel in performance of simple overlearned tasks (13). Postdrug increases in performance may be partially attributed to relearning occurring during the predrug testing.

The factor of sex of the experimenter may account for some differences between male and female subject performance. Studies have shown that subjects perform at a higher rate when the experimenter is of the opposite sex (14, 15). All subjects in this study were tested by the same female experimenter.

Sex-based differences in the performance of psychomotor tasks both initially and following drug treatment point out the need to consider the sex of the subject as an important factor in evaluating drug effects. Averaging the performance of an equal number of male and female subjects does not ensure results that can be generalized to both or, possibly, either sex. It may be inappropriate to generalize psychopharmacological research findings to the general population if only one sex has been used in the testing. Further study is indicated to determine if measurements other than psychomotor performance also show strong sex-based differences.

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Mathematical Description of Solute Velocities during Dissolution from a Horizontal Surface

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Abstract □ A mathematical analysis of solute flow in a descending column following dissolution is presented. The acceleration of a solute particle from zero velocity, when it is in the solid phase, to its final equilibrium descending velocity was analyzed. The maximum velocity for *N*-(3-methylphenyl)acetamide developed essentially at the solid–liquid interface, contradicting the postulate of a microsize diffusional layer. The possibility of a diffusional layer existing for solids of lower solubility than *N*-(3-methylphenyl)acetamide is discussed.

Keyphrases □ Solute velocities—in descending column during dissolution from a horizontal surface, mathematical analysis □ Velocities, solute—in descending column during dissolution from a horizontal surface, mathematical analysis □ Dissolution—from a horizontal surface, mathematical analysis of solute velocities in descending column

Studies utilizing a descending column model to investigate the dissolution of a solid showed that convective transport of solute rather than molecular diffusion is the primary means of mass transfer for such a model (1, 2). Interfacial effects such as solvent penetration, wetting, and solvation of the solid seem to control the rate of mass transfer when dissolution from the solid surface occurs in the descending direction. Under such conditions, one would not anticipate the presence of a finite "diffusion layer." Calculations based on measurements of the rate of movement of a solute front in a descending dissolution column (1) are presented here to show that steady-state velocities are established within microseconds and essentially begin at the interface, thus eliminating the possibility of a microsize diffusion layer.

THEORY AND DISCUSSION

The velocity of solute flow in a vertical dissolution column was determined from observations of the movement of the solute front down the column (1). Since a linear relationship was observed between the solvent front location and time, the velocity appears to be independent of time. There must, however, be a time-variant laminar flow velocity profile, on a molecular basis, for molecules in the bulk fluid stream at times close to zero. A molecule in the solid phase obviously has a zero-velocity component contributing to its flow down the column.

Following the solvation step in a dissolution process, the solvated solute molecule descends from rest in a stationary fluid under the action of gravity. The molecule first accelerates as it would in a vacuum; but unlike the situation in a vacuum, its acceleration is retarded due to friction with the surrounding solvent medium. As the frictional force increases with an increase in velocity, this force eventually reaches a value equal to that of the gravitational force. From that point on, the two forces are balanced and the molecule continues to fall at a constant velocity. The exponentially increasing velocity of such a molecule descending from rest under the influence of gravity represents an interesting first-order system, because the dynamics are defined completely by the steady-state velocity and the time constant for the approach to steady state can be predicted from this velocity.

Consider the fall of a solvated solute molecule through an aqueous medium when the solvated solute and solvent differ in density and viscosity. Under the action of gravity, the downward force, F, acting on the molecule depends on the relative magnitudes of the forces of gravity and buoyancy. The gravitational force, F_w, acts on the molecule even when it is at rest and remains constant during the entire period of descent. The buoyancy, F_b, is dependent on the solvent medium. From Newton's second law of motion:

$$F = F_w - F_b \qquad \text{(Eq. 1a)}$$

$$F = (\rho - \rho_0)gV \qquad \text{(Eq. 1b)}$$