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# Release and Elimination of $^{14}$C-Fluphenazine Enanthate and Decanoate Esters Administered in Sesame Oil to Dogs

**JACQUES DREYFUSS [x], JOHN J. ROSS, Jr., JAMES M. SHAW, IRVING MILLER, and ERIC C. SCHREIBER**

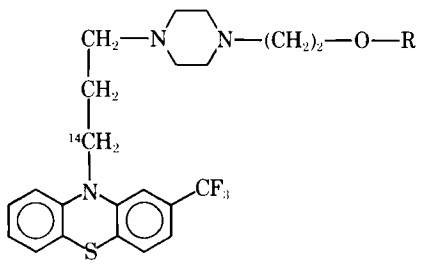
**Abstract** □ The rates of release of $^{14}$C-fluphenazine enanthate and $^{14}$C-fluphenazine decanoate were compared in two groups of five male dogs. Each dog was given a single dose (2 mg/kg im) of either the enanthate or decanoate ester in sesame oil. The times required to attain maximum concentrations of radioactivity in plasma were 3.8 ± 0.5 days (±*SE*) for the enanthate ester and 10.6 ± 1.1 days for the decanoate ester ($p < 0.001$); maximum concentrations of radioactivity in the plasma at these times were 16.7 ± 1.1 and 11.1 ± 1.2 ng/ml, respectively ($p < 0.01$). However, 35 days after dosing, the concentrations of radioactivity in plasma were greater for the decanoate ester than for the enanthate ester. The times required for 50% of the dose to be excreted in the urine and feces were 7.8 ± 0.5 days for the enanthate ester and 22.6 ± 4.4 days for the decanoate ester ($p < 0.05$). The total amounts excreted in 35 days were 85.4 ± 1.8 and 68.8 ± 6.6% of the dose for the enanthate and decanoate esters, respectively; the average half-times for the rates of release of radioactivity from depot and body, as calculated from the data for total excretion, were 5.55 days for the enanthate ester and 15.4 days for the decanoate ester. Thirty-five days after dosing, the amount of the dose present in the injection site was 4.6 ± 1.6% for the enanthate ester and 18.6 ± 5.7% for the decanoate ester. Two groups of six dogs each were protected against the emetic effects of apomorphine more than twice as long by the decanoate ester than by the enanthate ester after the subcutaneous administration of single 8-mg/kg doses of either drug in sesame oil ($p < 0.05$). Based on measurements of total radioactivity, it was concluded that the decanoate ester was released from the depot at less than one-half the rate of the enanthate ester.

**Keyphrases** □ Fluphenazine—enanthate and decanoate esters, rates of release and elimination in urine and feces, dogs □ Elimination—renal and GI, fluphenazine enanthate and decanoate esters, dogs

Although many studies conducted in humans have demonstrated the clinical efficacy of long-acting esters of fluphenazine, there is little objective evidence to enable one to quantitate their slow-release characteristics. Such studies are difficult to conduct in humans for the following reasons:

1. Sufficient radioactivity cannot be administered to humans to allow for the detection of the low concentrations of the drug or its metabolites present in the circulation during a prolonged time.
2. It is generally not feasible, even under the best of circumstances, to collect excreta quantitatively over a month, especially when most radioactivity is excreted in the feces as it is with fluphenazine and its esters (1–3).
3. At the conclusion of the study, it is not possible to determine the amount of drug remaining in the depot at the injection site.

The relative rates of release of the enanthate (I*a*) and decanoate (I*b*) esters of $^{14}$C-fluphenazine were compared in dogs because this species could be given



I*a*: R = $-C(=O)-(CH_2)_5CH_3$

I*b*: R = $-C(=O)-(CH_2)_8CH_3$

either ester (20 mg/0.5 ml of sesame oil) at approximately the same concentration as that most commonly given therapeutically to humans (25 mg/ml of sesame oil). Data published previously from studies of flupentixol decanoate indicate that the kinetics of drug release in dogs more closely resembles those found in humans than do the kinetics in rats (4).

## EXPERIMENTAL

$^{14}$C-Fluphenazine enanthate or decanoate had a specific activity of 4.92 or 4.84 μCi/mg, respectively. These compounds were not less than 97% chemically and radiochemically pure.

**Design**—Each ester (41 mg) was dissolved in 1.0 ml of sesame oil containing 1.6% benzyl alcohol. Two groups of five purebred male beagles each were injected intramuscularly into the *biceps femoris* of the thigh muscle (0.5 ml of drug formulation/10 kg) with either the enanthate or decanoate ester. The enanthate ester was given at an average dose of 1.89 ± 0.11 mg/kg (±*SE*); the decanoate was given at an average dose of 2.03 ± 0.04 mg/kg.

The dogs were housed in metabolism cages that permitted the separate collection of urine and feces. Blood samples were drawn periodically for 35 days, and the total urinary and fecal excretions were collected daily for 35 days. Then the dogs were sacrificed by anesthesia with pentobarbital (30 mg/kg iv), followed by the rapid injection of 5 ml of a saturated solution of potassium chloride.

The dogs were necropsied, and selected tissues were analyzed for the presence of residual radioactivity. In addition, the entire musculature of both the left and right thighs was excised and analyzed, so that the amount of radioactivity remaining in the injection site could be determined.

**Analysis of Plasma**—A 0.8-ml plasma sample was dissolved in 4 ml of solubilizer[1], and the sample was counted with 15 ml of toluene scintillation fluid. This scintillation fluid contained, per liter of toluene, 5 g of 2,5-diphenyloxazole and 300 mg of 1,4-bis[2-(4-methyl-5-phenyloxazolyl)]benzene.

**Analysis of Urine and Feces**—Fecal samples were homogenized with 2–3 volumes of methanol; about 800 mg of homogenate was combusted[2]. Urine samples (1 ml) were counted directly in 15 ml of Bray's scintillation fluid (5).

**Analysis of Tissues**—Brain samples were homogenized in water in an all-glass homogenizer[3]; about 800 mg of homogenate was combusted. Certain portions of the eye (lens, cornea, aqueous and vitreous humors, and combined retina, choroid, and sclera) were combusted. Similarly, representative portions of omental fat (200 mg) and skin without hair (200 mg) were combusted. Samples of tissue from the heart, kidneys, liver, lungs, and thigh muscle were ground in a meat grinder; then about 800 mg of each well-mixed sample was combusted.

**Counting of Samples**—Radioactivity in each sample was measured by a liquid scintillation spectrometer[4]. Counting efficiency was determined with automatic external standardization and the use of previously prepared quench curves.

**Duration of Protection against Apomorphine**—Mongrel dogs were selected that consistently responded to the emetic effect of apomorphine (20 μg/kg iv) after the ingestion of a test meal. Two groups of six dogs each (three males and three females per group) were given, at the nape of the neck, equimolar doses of fluphenazine enanthate (8.0 mg/kg sc) or fluphenazine decanoate (8.6 mg/kg sc) in sesame oil containing 1.5% benzyl alcohol (1.6 ml/10 kg). Two control dogs (one male and one female) were given only sesame oil.

On the day after dosing, all dogs were given 20 μg/kg of apomorphine, followed in 1 day by 640 μg/kg of apomorphine. All dogs treated with either fluphenazine ester were protected from emesis on both days, whereas the two control dogs vomited consistently. The dogs dosed with either fluphenazine ester were then challenged at weekly intervals with apomorphine (640 μg/kg iv). If no emesis occurred, the same dose of apomorphine was used the next week. If emesis occurred, the dogs were challenged again on the same day, about 6 hr later, with one-half the dose of apomorphine.

The emetic dose given the next week depended upon the response of the previous week but was generally decreased by 50% if emesis occurred at any given dose. When a dog treated with either fluphenazine ester vomited after being challenged with 20 μg/kg of apomorphine, it was considered to be no longer protected and was withdrawn from the study. The control dogs were challenged each week throughout the study with 20 μg/kg of apomorphine and consistently showed emetic responses.

**Analysis of Regression**—Data obtained for the presence of radioactivity in the plasma, urine, feces, and urine plus feces for each dog were subjected to an analysis of linear exponential regression. The objective at this stage was to find the time interval over which the greatest correlation coefficient ($r^2$) could be obtained. The half-time ($T_{1/2}$ = 0.693/slope × ln 10) for each parameter was computed from the slope of the line for each dog. The average $T_{1/2}$ for each parameter for each drug was obtained by pooling the individual data points over the time interval having the greatest $r^2$ for *each* dog.

An analysis of variance (ANOVA) for each pooled regression was performed to determine whether the slope of the regression line was significantly different from zero. It was significant in all cases ($p < 0.0001$). In addition, a test for linearity of the regression was performed by partitioning the residual sum of squares into the sum of squares for pure error and for lack of fit (6). An $F$-test was performed by dividing the mean square due to lack of fit by the mean square due to pure error. These results were also significant in all cases ($p < 0.05$).

The adequacy of the regression coefficients was further tested by an examination of residuals for: (*a*) outliers, (*b*) randomness when plotted against time, and (*c*) randomness when plotted against the predicted dependent variable. The 95% tolerance intervals were computed according to standard procedures.

**Tests for Correlation**—The correlation between the average regression lines for urinary and fecal excretion of radioactivity after dosing with each drug was determined by calculating the coefficients for Pearson's Product and Spearman's Rank Order (7).

**Analysis of Differences between Means**—Initially, the means of all parameters were compared by a one-way analysis of variance (ANOVA). The values cited (probability > $F$) indicate the $\alpha$-level of significance of the $F$-ratio for the hypothesis that the population means are equal. To determine whether the analysis of variance was valid, a test for the homogeneity of variances was performed (8). If the variances were equal ($p \leq 0.05$), the analysis of variance was considered valid. If the variances were unequal ($p \leq 0.05$), the analysis of variance was considered invalid and was replaced by a modified $t$-test (9).

## RESULTS

**Concentrations of Radioactivity in Plasma**—The concentrations of radioactivity in the plasma of dogs after intramuscular doses of either $^{14}$C-fluphenazine enanthate or decanoate are shown in Fig. 1. Concentrations of radioactivity were significantly different in the plasma of dogs given the enanthate or decanoate ester, except at 10, 13, and 16 days after dosing. One-half day after dogs had been dosed with the enanthate ester, greater concentrations of radioactivity were present in the plasma than in dogs dosed with the decanoate ester.

The maximum concentrations of radioactivity in plasma were greater and were attained earlier for the enanthate ester than for the decanoate ester. Thirty-five days after dosing with either ester, the concentrations of radioactivity in the plasma of the dogs dosed with the decanoate ester were significantly greater than they were in dogs given the enanthate ester.

Half-times of radioactivity in plasma were calculated as outlined under *Experimental*. The lines of best fit for the enanthate and decanoate esters, as obtained by analyses of regression, are shown in Fig. 2. The average half-lives obtained in this manner were 9.58 days for the enanthate ester and 33.6 days for the decanoate ester. Although the correlation coefficients obtained after dosing with the enanthate ester were slightly higher on the average when the time interval of 3–24 days was used, it was decided to extend the time interval to 35 days, thereby facilitating the comparison of the enanthate ester with the decanoate ester. In fact, this extension

[1] NCS solubilizer, Amersham/Searle Corp., Des Plaines, Ill.
[2] R. J. Harvey Instrument Corp., Hillsdale, N.J.
[3] Potter-Elvehjem, Fisher Scientific Co., Springfield, N.J.
[4] Packard Tri-Carb model 3380, Packard Instrument Co., Downers Grove, Ill.

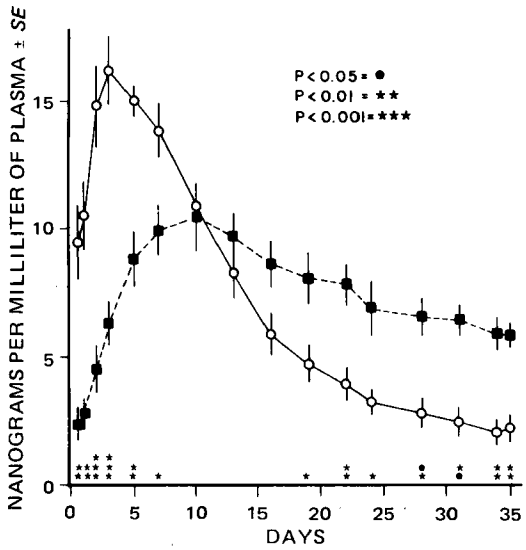



**Figure 1**—*Average concentrations of radioactivity in the plasma of dogs after the intramuscular administration of either fluphenazine enanthate or fluphenazine decanoate. Key:* ■, *$^{14}$C-fluphenazine decanoate; and* O, *$^{14}$C-fluphenazine enanthate.*

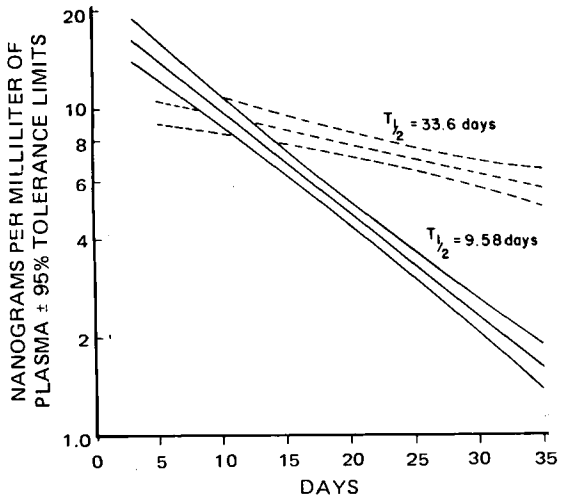



**Figure 2**—*Line of best fit and 95% tolerance limits for concentrations of radioactivity in the plasma of dogs dosed with either fluphenazine enanthate or fluphenazine decanoate. Key: - - -, $^{14}$C-fluphenazine decanoate; and —, $^{14}$C-fluphenazine enanthate.*

had only a minor effect on the half-lives obtained (8.38 *versus* 9.58 days).

**Excretion of Radioactivity in the Urine and Feces**—Urine and feces from each dog dosed with either ester were collected daily for 35 days. The average excretion of radioactivity by dogs dosed with either ester was mostly in the feces (66–81% of the dose); on the average, only 3–4% of the dose was excreted in the urine (Fig. 3). During the 35-day test, totals of 85 and 69% of the dose were excreted by dogs dosed with the enanthate and decanoate esters, respectively.

Lines of best fit were calculated for each ester for the total excretion of radioactivity. The total excretion of radioactivity (Fig. 4) indicated an average half-life of 5.55 days for the enanthate ester and 15.4 days for the decanoate ester. Figure 5 shows lines of best fit for the urinary and fecal excretion of radioactivity for each ester. The average slopes of the lines of best fit for the excretion of radioactivity in the urine and feces for each ester are parallel, as evidenced by the similar magnitude of the half-lives.

Correlation between the slopes for the urinary and fecal excretion of radioactivity by *each dog* dosed with either ester was statistically significant ($p < 0.0004$). We consider it very significant that

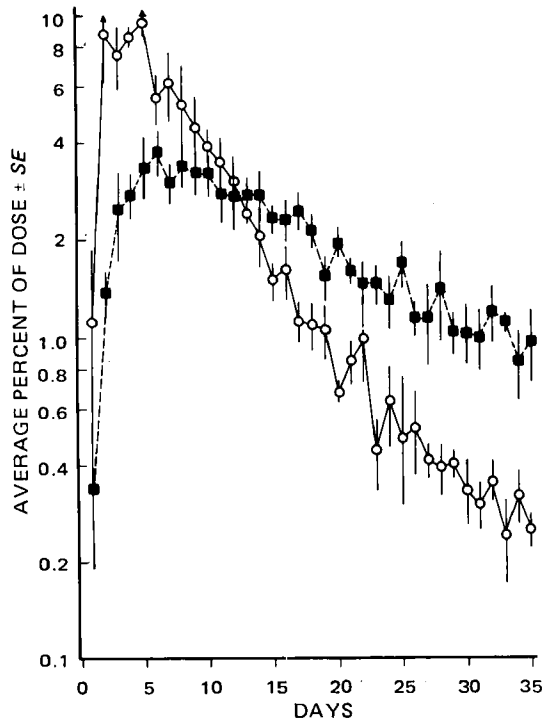



**Figure 3**—*Average daily excretion of radioactivity in the urine and feces of dogs after the intramuscular administration of either fluphenazine enanthate or fluphenazine decanoate. Key:* ■, *$^{14}$C-fluphenazine decanoate; and* O, *$^{14}$C-fluphenazine enanthate.*

the sets of lines, representing the enanthate and decanoate esters, have the same slope, even though one regression line represents urinary excretion and the other represents fecal excretion. In addition, the magnitudes of the slopes for each excretory route were different for the two esters.

Another way of comparing the rates of excretion of radioactivity for the two esters is by grouping the data on a weekly basis. Table I shows the amounts of radioactivity excreted on a weekly basis for each ester beginning with zero time and not just including the descending portion of each plot for excretion. The data clearly indicate, with high statistical significance, that the rate of release of radioactivity was greatest for the enanthate during the 1st week

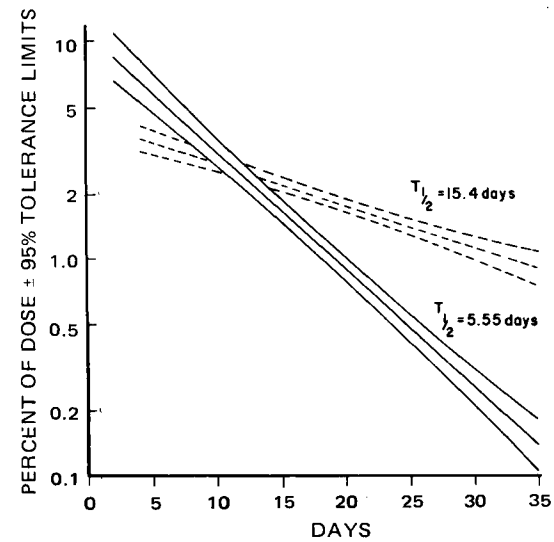



**Figure 4**—*Line of best fit and 95% tolerance limits for the total excretion of radioactivity by dogs after the intramuscular administration of either fluphenazine enanthate or fluphenazine decanoate. Key: - - -, $^{14}$C-fluphenazine decanoate; and —, $^{14}$C-fluphenazine enanthate.*

**Table I—Weekly Excretion of Radioactivity after the Intramuscular Administration to Dogs of Either Fluphenazine Enanthate or Fluphenazine Decanoate**

| Weeks | Total Excretion, % of Dose ± *SE* | | Statistical Significance |
|---|---|---|---|
| | Enanthate | Decanoate | |
| 1 | 46.98 ± 2.62 | 17.07 ± 2.36 | $p < 0.0001$ |
| 2 | 24.48 ± 1.76 | 20.80 ± 2.68 | $p < 0.28$ |
| 3 | 7.87 ± 0.50 | 14.25 ± 1.06 | $p < 0.0009$ |
| 4 | 3.95 ± 0.48 | 9.55 ± 0.86 | $p < 0.0007$ |
| 5 | 2.12 ± 0.30 | 7.13 ± 0.32 | $p < 0.0001$ |

after dosing but was greatest for the decanoate during the 2nd week after dosing. The data for both esters were not significantly different during the 2nd week, since the two curves cross each other at that time.

**Residual Radioactivity in Selected Tissues and Drug Depot**—The dogs were sacrificed 35 days after receiving either ester, and selected tissues were analyzed for residual radioactivity (Table II). In addition, the entire left thigh muscle of each dog, into which the drug had been injected, was excised and homogenized to determine how much radioactivity was still present in the depot. The right thigh muscle of each dog was processed similarly to provide a measure of the amounts of radioactivity that would ordinarily have localized in muscle from the presence of the drug in the circulation.

In dogs dosed with either ester, only traces of radioactivity were present in the blood, brain, nonpigmented portions of the eye, kidneys, omental fat, skin, and right thigh muscle. More appreciable amounts of radioactivity were found in the combined retina, choroid, and sclera of the eye, the liver, and the left thigh muscle. The binding of the phenothiazines to melanin is a well-established phenomenon (10, 11). The localization of radioactivity in the liver can be related to the biliary elimination of the fluphenazine esters.

Thirty-five days after dosing, radioactivity was still present in the injection sites of both groups of dogs: an average of about 5% of the dose for the enanthate ester and of about 19% for the decanoate ester. These amounts correlate with their relative rates of release from the depot, as evidenced by the relative half-times for excretion, and with their rates of release of radioactivity into the circulation.

**Studies with Apomorphine**—Pharmacological studies in dogs utilized the apomorphine test to determine the duration of action of long-acting neuroleptics. The decanoate ester protected dogs longer than did the enanthate ester ($p < 0.01$ for the response to 640 μg/kg of apomorphine by a Wilcoxon Rank Sum Test) (Table III). The ratio of protection against emesis (decanoate ester–enanthate ester) at any dose of apomorphine was slightly greater than 2. In addition, the decrease in the logarithm of the apomorphine dose with time was determined for each dog after dosing. The average slope, as determined from lines of best fit for *each dog*, was 2.88 times greater for the enanthate ester than for the decanoate ester ($p \leq 0.05$ by the Wilcoxon Rank Sum Test).

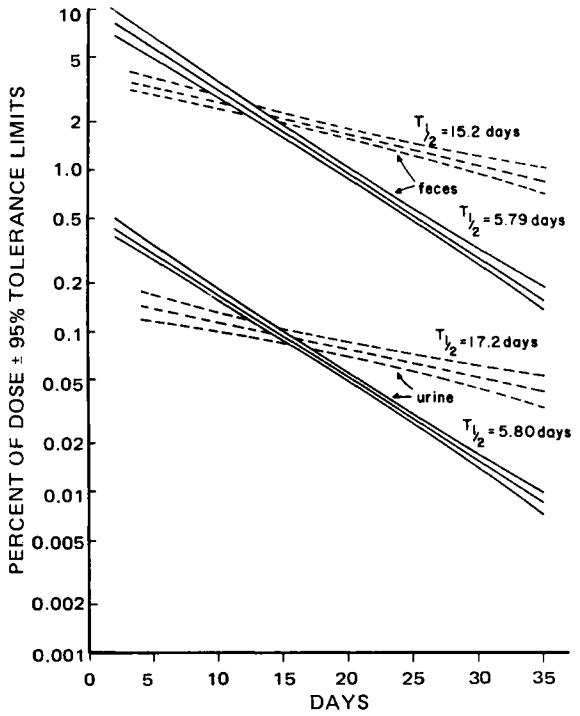



**Figure 5**—*Lines of best fit and 95% tolerance limits for the excretion of radioactivity in the urine or feces after the intramuscular administration of either fluphenazine enanthate or fluphenazine decanoate. Key: - - -, $^{14}C$-fluphenazine decanoate; and —, $^{14}C$-fluphenazine enanthate.*

## DISCUSSION

A comparison of selected parameters for each dog given either $^{14}C$-fluphenazine enanthate or $^{14}C$-fluphenazine decanoate is shown in Table IV. This table shows arithmetic averages for each parameter and the statistical significance of the difference between each pair of values. During the entire study, 88–91% of the dose could be accounted for by the amounts of radioactivity excreted, the amounts present in the depot after 35 days, and the amounts remaining in certain tissues.

**Table II—Average Residual Radioactivity Present in Selected Tissues of Dogs 35 Days after the Intramuscular Administration of Either Fluphenazine Enanthate or Fluphenazine Decanoate**

| Tissue | Fluphenazine Enanthate[a] | | Fluphenazine Decanoate[a] | |
|---|---|---|---|---|
| | μg/g ± *SE* | % of Dose ± *SE* | μg/g ± *SE* | % of Dose ± *SE* |
| Brain | 0.005 ± 0.001 | 0.002 ± 0.000 | 0.013 ± 0.002 | 0.004 ± 0.001 |
| Combined retina, choroid, and sclera | 0.53 ± 0.15 | — | 0.57 ± 0.17 | — |
| Cornea | 0.26 ± 0.23 | — | 0.022 ± 0.007 | — |
| Aqueous humor | 0.002 ± 0.001 | — | 0.004 ± 0.003 | — |
| Vitreous humor | 0.039 ± 0.020 | — | 0.030 ± 0.017 | — |
| Lens | 0.002 ± 0.001 | — | 0.003 ± 0.001 | — |
| Kidneys | 0.032 ± 0.004 | 0.010 ± 0.001 | 0.042 ± 0.009 | 0.010 ± 0.003 |
| Liver | 0.25 ± 0.05 | 0.46 ± 0.08 | 0.34 ± 0.05 | 0.49 ± 0.06 |
| Omental fat | 0.001 ± 0.001 | — | 0.011 ± 0.004 | — |
| Skin | 0.035 ± 0.008 | — | 0.032 ± 0.010 | — |
| Left thigh muscle (contains injection site) | 1.66 ± 0.52 | 4.65 ± 1.63 | 7.97 ± 2.34 | 18.66 ± 5.70 |
| Right thigh muscle | 0.009 ± 0.005 | 0.024 ± 0.011 | 0.021 ± 0.011 | 0.048 ± 0.023 |
| Blood, μg/ml | 0.001 ± 0.000 | — | 0.003 ± 0.001 | — |

[a] $n = 5$.

**Table III—Protection against the Emetic Effect of Apomorphine Provided by Either Fluphenazine Enanthate or Fluphenazine Decanoate Administered Subcutaneously to Dogs**

| Dose of Apomorphine, μg/kg iv | Duration of Protection against Emesis (First Time for Emesis), Days ± *SE* | | Ratio of Protective Effect, Decanoate/Enanthate |
|---|---|---|---|
| | Fluphenazine Enanthate[a] | Fluphenazine Decanoate[b] | |
| 20 | 55 ± 6 | 124 ± 11[c] | 2.25 |
| 40 | 46 ± 3 | 105 ± 7 | 2.31 |
| 80 | 45 ± 3 | 91 ± 8 | 2.02 |
| 160 | 40 ± 3 | 87 ± 9 | 2.18 |
| 320 | 38 ± 3 | 82 ± 9 | 2.16 |
| 640 | 34 ± 2 | 74 ± 6 | 2.18 |

[a] Using 8.0 mg/kg sc in 1.6 ml of sesame oil/10 kg of body weight. [b] Using 8.6 mg/kg sc in 1.6 ml of sesame oil/10 kg of body weight. [c] Two of the six dogs tested at this dose were still protected against the emetic effects of apomorphine 148 days after dosing.

The data of Table V show a complete comparison of the relevant half-times for release of radioactivity from the depot and the body for each ester, as calculated from the pooled regression data, rather than as the arithmetic averages. These data, based on measurements of total radioactivity, indicate that the decanoate ester was released at considerably less than one-half the rate of the enanthate ester. It is not clear why the half-times in plasma and excreta differed by a factor of almost 2. This finding might be explained by the inability to measure either unchanged parent ester. The possibility exists that the rate of excretion of radioactivity reflects the excretion of a metabolite, whereas the elimination of radioactivity from the plasma represents some combination of the elimination of the parent compound and a metabolite. However, in spite of this difference in absolute half-times between that found in plasma and excreta for both esters, the *ratio* of half-times for the decanoate–enanthate in plasma was still about 3:1.

The fact that the slopes of the regression lines for the urinary and fecal excretion of the enanthate and decanoate esters are similar for each drug, but different between the two drugs, suggests that the release of radioactivity from the oily depot may be the controlling factor that accounts for the different rates at which these esters are released from their sites of injection. However, other possibilities are not excluded by this finding of parallel slopes; *e.g.*, the hydrolysis of the ester bound could be the rate-limiting step.

**Table V—Average Half-Times of Radioactivity in the Plasma and Excreta of Dogs after the Intramuscular Administration of Either Fluphenazine Enanthate or Fluphenazine Decanoate**

| Sample | $T_{1/2}$, Days | | $T_{1/2}$ Decanoate |
|---|---|---|---|
| | Enanthate | Decanoate | $T_{1/2}$ Enanthate |
| Plasma | 9.58 | 33.56 | 3.51 |
| Urine | 5.80 | 17.15 | 2.96 |
| Feces | 5.79 | 15.23 | 2.63 |
| Urine + feces | 5.55 | 15.39 | 2.77 |

Studies to answer this question were conducted recently and will be reported separately. Briefly, anesthetized dogs, whose bile ducts had been cannulated, were given intravenous doses of either the enanthate or decanoate ester of fluphenazine (1 mg/kg; unformulated). No unchanged $^{14}$C-fluphenazine enanthate or $^{14}$C-fluphenazine decanoate was present in the bile of these dogs in the earliest sample collected (0–1 hr). In addition, a large sample of blood was removed from the dogs 30 min after they had been dosed; extraction and chromatography of the plasma indicated that at least 79% of the radioactivity had been converted to free fluphenazine or its metabolites.

Moreover, when intravenous doses of either fluphenazine or its enanthate and decanoate esters were given to intact dogs (1 mg/kg), no sustained-release effect was obtained and similar concentrations of radioactivity were found in plasma. The kinetics of elimination of this radioactivity in plasma and its excretion in urine and feces were also comparable for all three compounds. These experiments demonstrate that the dog can rapidly hydrolyze either of these two esters and implicate the presence of the drugs in an oily depot as being responsible for sustained release. Earlier published findings on the disposition of $^{14}$C-fluphenazine enanthate in dogs (1 mg/kg iv) also are consistent with this conclusion (2).

A difference between the duration of action of the decanoate ester relative to that of the enanthate ester in both the apomorphine test and the rates of release of radioactivity from the depot could be due to at least two factors. First, in the apomorphine study, the esters were administered subcutaneously rather than intramuscularly. Second, the volume of sesame oil given intramuscularly (0.5 ml/10 kg) was less than the volume given subcutaneously (1.6 ml/10 kg).

Studies of conditioned avoidance behavior in rats given single doses of either fluphenazine enanthate or decanoate revealed the

**Table IV—Comparison of Selected Parameters after the Intramuscular Administration to Dogs of Either Fluphenazine Enanthate or Fluphenazine Decanoate in Sesame Oil**

| Parameter | Fluphenazine Enanthate | Fluphenazine Decanoate | Statistical Significance of the Difference between Means |
|---|---|---|---|
| Plasma concentration at 0.5 day, ng/ml | 9.5 ± 1.5[a] | 2.3 ± 0.7 | $p < 0.005$ |
| Time required to attain maximum plasma concentration, days | 3.8 ± 0.5 | 10.6 ± 1.1 | $p < 0.001$ |
| Maximum plasma concentration, ng/ml | 16.7 ± 1.1 | 11.1 ± 1.2 | $p < 0.01$ |
| Plasma concentration at 35 days, ng/ml | 2.2 ± 0.5 | 6.1 ± 0.4 | $p < 0.001$ |
| Plasma half-time, days | 9.58 ± 0.70 | 33.1 ± 3.9 | $p < 0.01$ |
| Urinary half-time, days | 5.74 ± 0.50 | 11.7 ± 2.4 | N.S.[b] |
| Fecal half-time, days | 5.55 ± 0.39 | 13.8 ± 2.1 | $p < 0.02$ |
| Total excretion half-time, days | 5.01 ± 0.54 | 13.7 ± 2.1 | $p < 0.02$ |
| Time required for 50% of dose to be excreted, days | 7.8 ± 0.5 | 22.6 ± 4.4 | $p < 0.05$ |
| Amount of radioactivity excreted in urine in 35 days, % of dose | 4.11 ± 0.13 | 2.96 ± 0.45 | N.S. |
| Amount of radioactivity excreted in feces in 35 days, % of dose | 81.29 ± 1.77 | 65.84 ± 6.33 | N.S. |
| Amount of dose excreted in 35 days, % | 85.40 ± 1.75 | 68.80 ± 6.63 | N.S. |
| Amount of dose found in injection site after 35 days, % | 4.62 ± 1.64 | 18.61 ± 5.71 | $p < 0.1$ |
| Total amount of dose recovered during entire study, %[c] | 90.56 ± 1.10 | 88.04 ± 2.55 | N.S. |

[a] All values are the averages ± *SE*. [b] N.S. = not significant. [c] Includes the amounts present in certain tissues that contained residual radioactivity.

same spectrum of activity for both esters but a longer duration of action for the decanoate (12). Nymark *et al.* (13) reported on the prolonged neuroleptic effect of α-flupentixol decanoate in oil[5]. Subcutaneous doses of α-flupentixol decanoate provided protection against the emetic effects of apomorphine for 18–21 days, whereas comparable doses of α-flupentixol in oil provided protection for only 2–3 days. Nymark *et al.* (13) presumed that the decanoic acid ester of α-flupentixol, which is several thousand times more lipophilic than α-flupentixol, releases drug at a slower rate from the oily depot.

A comparison of concentrations of radioactivity in blood after the intramuscular injection of flupentixol decanoate into rats, dogs, or humans indicated that species differences exist in the rate of drug release from the depot (11). Rats and humans seemed to differ greatly in their relative rates of release, while dogs and humans apparently were more alike. These investigators (11) speculated that factors such as the different injection volumes leading to different degrees of spreading of the injected oil, as well as differences in blood flow through the injected muscle, may contribute to these observed species differences.

In studies of metabolism of flupentixol decanoate in rats and dogs, these two species behaved differently with respect to the rate at which the drug was released from an oily depot (14). Thus, rats showed maximum concentrations of radioactivity in blood within the first 24 hr after intramuscular dosing, whereas the maximum concentrations of radioactivity in blood of dogs were obtained 7 days after intramuscular dosing. These investigators (14) speculated that, since rats received a relatively greater volume of oil than did dogs, differences in the rates of release of drug from the depot were probably responsible for these varied effects.

Support for this concept is provided by an earlier study on the duration of action of subcutaneously administered testosterone and its propionate ester (15). That study showed that the amount of sesame oil used as a vehicle for the subcutaneous injection of testosterone or its propionate ester affected the duration of action of these two steroids. In the case of testosterone, sustained biological activity was prevented by the larger, and favored by the smaller, volume of oil. In the case of testosterone propionate, the larger volume of oil prolonged and intensified the compound's activity.

These investigators (15) pointed out that several factors can determine the rate of absorption of compounds from subcutaneous or intramuscular depots, including: (*a*) the absorbing area, which is proportional to the amount of solvent injected; (*b*) the ability, if any, of the solvent to bind the compound; (*c*) the rate at which the compound is released from the solvent; and (*d*) the rate at which the solvent itself is absorbed. In the case of the fluphenazine esters dissolved in sesame oil, it is not known which factors are involved in the difference in the rates of release of the enanthate and the decanoate from an oily depot.

Interesting studies have been published on some long-acting esters of pipotiazine (16). In rats that received intramuscular injections of pipotiazine palmitate and that were studied for 80 days, about 95% of the radioactivity present in the organism at any time was found in the region of the leg where the drug had been injected originally. Jørgensen *et al.* (14) reported similar observations for flupentixol decanoate. These observations provide further support for the idea that the prolonged duration of action of these compounds results primarily from their slow release from an oily depot.

Studies *in vitro* have shown that esterases in the plasma or tissues of the rat or dog are capable of hydrolyzing either the undecylenic or palmitic ester of pipotiazine (16), flupentixol decanoate (14), fluphenazine enanthate (2, 3), or fluphenazine decanoate[6]. From these studies, one can reasonably conclude that the parent neuroleptic molecule, rather than the intact ester, is responsible for the pharmacological action of these drugs.

[5] Viscoleo.

[6] J. Dreyfuss and J. M. Shaw, unpublished data.

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