special case in which all doses after the first dose of each treatment are skipped to permit more extensive sampling of ω. Conversely, the proposed method may be thought of as a salvage operation for planned steady-state comparisons that fall short of target and for planned single-dose studies where the washout period is too short.

APPENDIX

The validity of Eq. 5 (and, therefore, Eqs. 16 and 28) can be demonstrated with a set of simulated data generated with the aid of a one-compartment open model, in which $F_I = 0.8$, $F_{II} = 0.6$, $k_a = 1.0$ hr^{-1}, $\omega = 0.015$ hr^{-1}, and $V_0 = 10$ liters in accordance with the prescribed regimen. Under these circumstances, the correction factor $\phi(1 - e^{-\omega\tau_1})/\tau_1(1 - e^{-\omega\phi})$ is 1.139; the residue factor W is 0.096; and the regimen factors $R_I = 2.334$, $R_I' = 2.528$, and $R_{II} = 0.920$. Given $D_I = 25$ mg, $D_{II} = 75$ mg, $\bar{C}p^{(I,\tau_1)} = 0.15$ μg/ml, and $\bar{C}p^{(II,\phi)} = 0.13$ μg/ml, $F_{II}/F_I = 0.75$.

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Effect of Formulation of Intramuscular Injections of Phenothiazines on Duration of Activity

A. T. FLORENCE [x], A. W. JENKINS [*], and A. H. LOVELESS

Abstract □ Trifluoperazine and pericyazine were formulated using both the hydrochloride and embonate salts, and some comparisons were made with the activity of fluphenazine salt and ester formulations. Simple solutions in polyethylene glycol, gelled aqueous solutions, nonaqueous suspensions, multiple emulsions, and microencapsulated preparations were formulated, and their duration of activity was tested in dogs. While the multiple emulsion system showed some promise, a nylon microcapsule system produced significant prolonged activity of the drug after deep intramuscular injection.

Keyphrases □ Phenothiazines—effect of various pharmaceutical formulations on duration of biological activity, dogs □ Trifluoperazine hydrochloride and embonate—effect of various pharmaceutical formulations on duration of biological activity, dogs □ Pericyazine embonate—effect of various pharmaceutical formulations on duration of biological activity, dogs □ Pharmaceutical formulations, various—phenothiazines, effect on duration of biological activity, dogs □ Tranquilizers—trifluoperazine hydrochloride and embonate and pericyazine embonate, effect of various pharmaceutical formulations on duration of biological activity, dogs

Long-acting injectable phenothiazines are valuable in extended aftercare therapy in certain psychiatric states (1, 2). Currently available long-acting neuroleptics include solutions in oils such as sesame oil of poorly water-soluble esters of fluphenazine[1] and flupentixol[2], the duration of activity being up to 40 days. However, not all phenothiazines can be esterified to form lipid-soluble derivatives. Therefore, this work was directed toward alternative methods of prolonging the activity of two such drugs, trifluoperazine and pericyazine, using physicochemical rather than chemical or pharmacological methods.

Various formulation techniques, similar to those reviewed by Ritschel (3), were utilized. Resulting preparations were tested in dogs by an apomorphine challenge test utilizing the antiemetic as opposed to the tranquilizing properties of the phenothiazine, since levels of phenothiazine attained cannot be measured readily by available chemical assay techniques. Some experiments were carried out for comparative purposes using fluphenazine embonate. In all cases, fluphenazine enanthate in sesame oil was used as a reference formulation.

EXPERIMENTAL

Materials—Trifluoperazine hydrochloride and embonate salts[3] and pericyazine embonate[3] were used as received. Fluphenazine embonate was recovered after mixing equimolar solutions of sodium embonate[4] and fluphenazine hydrochloride[5]. Fluphenazine enanthate in sesame oil[6] (25 mg/ml) was obtained commercially.

Drug Solubilities—The solubilities of the bases were determined by a turbidity method (4). The solubilized embonate salts were determined by a modification of this method. Various solutions of drug hydrochloride were mixed with buffered sodium embonate (pamoate) to give equimolar mixtures. The turbidity of the solutions at 560 nm was plotted against the final concentration of drug embonate in the

[1] Moditen and Moditen Enanthate, Modecate; Squibb, United Kingdom; Prolixin Enanthate, Squibb, Princeton, N.J.

[2] Depixol, Lundbeck.

[3] May and Baker, Dagenham, Essex, United Kingdom.

[4] Eastman Kodak.

[5] Donated by Squibb, United Kingdom.

[6] Moditen, Squibb.

Table I—Formulation Compositions and Summary of Biological Results

Drug	Formulation	Drug Concentration in Formulation, mg/ml	Administered Dose[a], mg/kg	Duration of Total Inhibition of Retching, days	Time for Return to 25% Control Response, days
Trifluoperazine hydrochloride	5% Bentonite aqueous gel	100	2.5	1	8.5
	35% Polysorbate 80 aqueous gel	100	2.5	1	6
	Multiple emulsion	20	2.5	1	10
			5	3	21
Trifluoperazine embonate	Suspension in 1% aluminum stearate–gelled sesame oil	100	5	1	6.5
	Solution in polyethylene glycol 400	100	5	1	9
	Solution in polyethylene glycol 600	100	5	—	14.5
			5	3	17.5
	Sesame oil suspension of microencapsulated polyethylene glycol 400 drug solution	30	10	3	21
Pericyazine embonate	Suspension in 1% aluminum stearate–gelled sesame oil	100	5	1	6.5
	Solution in polyethylene glycol 400	100	5	1	5.5
	Solution in polyethylene glycol 600	100	5	1	5
	Aqueous suspension of microencapsulated polyethylene glycol 400–aqueous (50:50) mixture drug solution	30	5	Total inhibition	19
			5	not achieved	19
	Sesame oil suspension of microencapsulated polyethylene glycol 400–aqueous (50:50) mixture drug solution	30	10	Total inhibition not achieved	23
Fluphenazine embonate	Solution in polyethylene glycol 400	100	2	1	11
Fluphenazine enanthate	Solution in sesame oil	25	2	7	28
			0.8	3	21
			0.2	3	11.5

[a] Approximate dose equivalents as regards antiemetic activity: 2.5 mg of trifluoperazine hydrochloride/kg ≡ 5 mg of trifluoperazine embonate/kg ≡ 5 mg of pericyazine embonate/kg ≡ 2 mg of fluphenazine embonate/kg ≡ 1.5 mg of fluphenazine enanthate/kg.

buffered solution, and extrapolation to zero turbidity gave the solubility value.

Sample Preparation—All samples contained from 20 to 100 mg of drug/ml. Due to its relative instability, the multiple emulsion containing trifluoperazine hydrochloride was prepared immediately prior to use; the other preparations were inherently stable (Table I).

Aqueous Gels—Aqueous solutions of trifluoperazine hydrochloride were gelled by incorporation into solutions of 5% bentonite, 35% polysorbate 80, or up to 5% povidone (molecular weight 44,000) to give gels containing 100 mg of drug/ml.

Solutions—Solutions of drug embonates were prepared in liquid polyethylene glycols 400 and 600.

Suspensions—Powdered drugs, either as the hydrochloride (trifluoperazine) or embonate (pericyazine and trifluoperazine), were dispersed in sesame oil by grinding in a mortar.

Multiple Emulsions—Multiple emulsions were prepared as follows. An aqueous solution of trifluoperazine hydrochloride (2.75 g) in 15 ml of water containing polysorbate 85[7] (0.6 g) in sesame oil (40 ml containing 2.4 g of sorbitan trioleate[8]) was redispersed in an aqueous 5% polysorbate 40[9] solution to give a water-in-oil in water multiple emulsion containing 20 mg/ml of trifluoperazine hydrochloride.

Microcapsule Formulations—These formulations were prepared using an interfacial polymerization process in which the drug embonates were dissolved in polyethylene glycol 400. This process was described in detail elsewhere (5), and the properties of the microcapsules were discussed previously (6).

Formulation Evaluation *In Vivo*—Four beagle dogs of either sex, 10–17 kg, were injected with apomorphine, 0.1 mg/kg sc, on three occasions during the week before the test compound was administered. The number of retches occurring in the 30 min after dosing was counted. Two days after the final control session, the test formulation was administered by deep intramuscular injection into the thigh at a dose of 2.5, 5, or 10 mg/kg. After 24 hr, 3 days, 7 days, and weekly intervals, the apomorphine challenge was repeated.

The number of retches of all four dogs receiving a particular phenothiazine preparation was averaged and compared to the prephenothiazine response. Results are expressed as the percentage of prephenothiazine response that the apomorphine challenge stimulated and were plotted against the number of days after the phenothiazine was administered. Standard errors of the results from four dogs receiving the same dose of phenothiazine were from ±12 to ±15%.

[7] Tween 85, Atlas, supplied by Honeywill-Atlas, Surrey, England.
[8] Span 85, Atlas, supplied by Honeywill-Atlas, Surrey, England.
[9] Tween 40, Atlas, supplied by Honeywill-Atlas, Surrey, England.

RESULTS

The results in Fig. 1 can be considered as a baseline with which to gauge the success of other formulations. It could be anticipated that solutions of trifluoperazine and pericyazine embonates might be relatively short acting. However, the nature of the glycol vehicle might be expected to influence the duration of activity. The use of a suspension of the drug embonate in sesame oil (in which the drug is virtually insoluble) also might have influenced the result.

Figure 1 shows that there was no appreciable advantage in using a solution of poorly water-soluble salts such as the embonates to prolong activity beyond a few days, since the duration of activity shown was of the same order as that from an aqueous injection of trifluoperazine hydrochloride. Trifluoperazine embonate apparently was longer acting than pericyazine embonate, but this result may simply have been a reflection of the greater potency of the former drug. Because the two drugs have similar physicochemical characteristics, the reversal of the order of results for the two polyethylene glycol solutions and the dispersion (Fig. 1) was seen as a reflection of the experimental error in the assay.

The results obtained with sesame oil solutions of fluphenazine enanthate at various doses and with fluphenazine embonate in polyethylene glycol solution are shown in Fig. 2. These results show that: (*a*) the duration of activity of fluphenazine enanthate at 2 mg/kg, *i.e.*, 28 days, was comparable with the normal maximum clinical response; and (*b*) fluphenazine itself had no inherent prolonged activity, because fluphenazine embonate in glycol solution showed no significant difference in duration of activity from the embonate solutions of trifluoperazine and pericyazine (Fig. 1). This finding is in agreement with that of Laffan *et al.* (7).

Formulation of trifluoperazine hydrochloride as a multiple emulsion, thereby creating an interfacial barrier to drug diffusion, yielded more promising results (Fig. 3). At both 2.5 and 5 mg/kg, activity was prolonged, although complete inhibition of retching was of limited

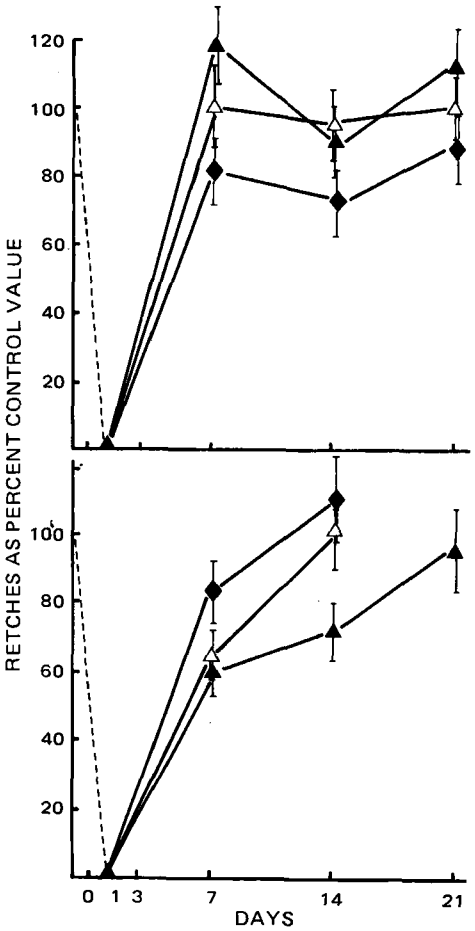

Figure 1—*(Top) Duration of activity of intramuscular injections of pericyazine embonate (5 mg/kg) as a solution in polyethylene glycol 400 (△), a solution in polyethylene glycol 600 (▲), and a dispersion of drug in sesame oil (♦). (Bottom) Duration of activity of intramuscular injection of trifluoperazine embonate (5 mg/kg) as a solution in polyethylene glycol 400 (△), a solution in polyethylene glycol 600 (▲), and a dispersion of drug and sesame oil (♦).*

duration. At 5 mg/kg, complete inhibition of the retching response was extended to 3 days and was followed by a more gradual return to the predrug response (Fig. 3). The polysorbate 80 gel formulation (Fig. 3) had no advantage over a solution of the embonate in polyethylene glycol; it was too rapidly dispersed from the injection site. The bentonite gel formulation, which had a slow release pattern *in vitro*, displayed a slightly longer activity than the polyethylene glycol solutions, but this finding was not sufficient to encourage further work on the formulation. This result led to the realization that a more efficient and more stable barrier to drug diffusion was required, so microencapsulation of the drug solution was attempted.

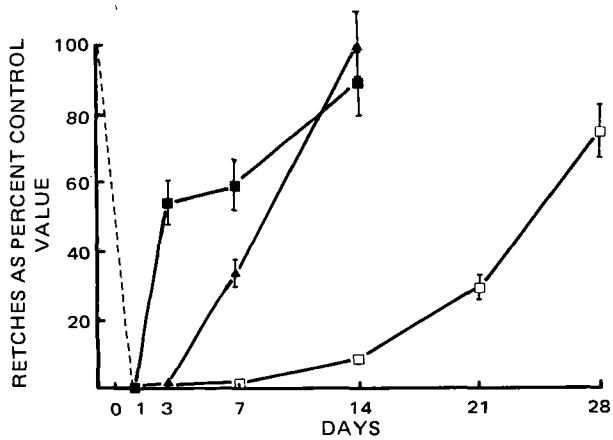

Figure 2—*Duration of activity of fluphenazine preparations. Key: ■, fluphenazine embonate solution in polyethylene glycol 400 (2 mg/kg); ▲, fluphenazine enanthate solution in sesame oil (0.2 mg/kg); and □, fluphenazine enanthate solution in sesame oil (2 mg/kg).*

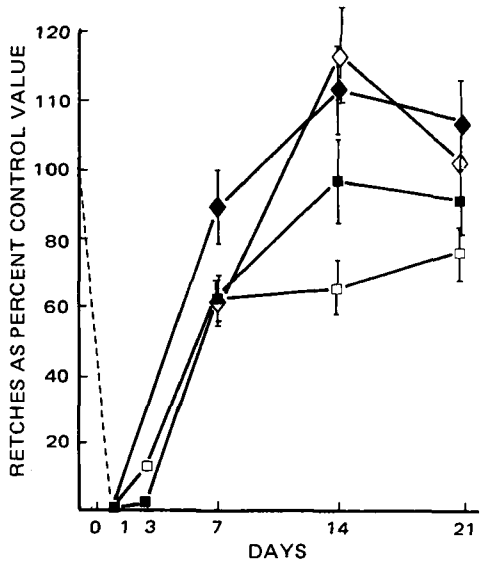

Figure 3—*Results for various formulations of trifluoperazine hydrochloride. Key: ◊, 2.5 mg/kg of drug in bentonite gel; ♦, 2.5 mg/kg of drug in polysorbate 80 gel; □, 2.5 mg/kg of drug in multiple emulsion; and ■, 5.0 mg/kg of drug in multiple emulsion.*

Results with a microencapsulated pericyazine embonate in 50% polyethylene glycol 400 aqueous solution are presented in Fig. 4. Insufficient drug was released initially to give complete inhibition of drug response on Day 1, as was obtained with all previous formulations. Doubling the injected dose increased the response up to 2 weeks. This result was more pronounced when an additional barrier in the form of the sesame oil suspending vehicle was present. However, after 2 weeks, by which time the sesame oil was removed from the injection site, no significant difference between the two preparations was observed. Microencapsulation of a polyethylene glycol 400 solution of trifluoperazine embonate resulted in a more satisfactory response–time profile (Fig. 4), where the time for return to predrug response was about 28 days.

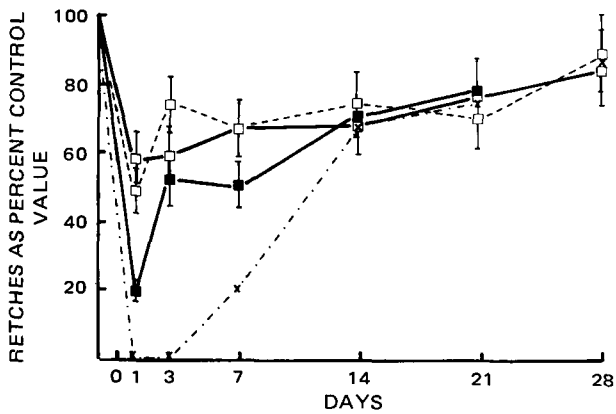

Figure 4—*Results for microencapsulated preparations of pericyazine embonate and trifluoperazine embonate. Key: □—□, pericyazine microencapsulated in nylon 610 (dose 5 mg/kg), with the microcapsule suspension being injected intramuscularly as a suspension in sesame oil; □- -□, pericyazine microencapsulated in nylon 610 (dose 10 mg/kg), with the microcapsule suspension being injected intramuscularly as a suspension in sesame oil; ■—■, pericyazine microencapsulated in nylon 610 (dose 5 mg/kg), with the preparation being injected as an aqueous suspension; and ×- -×-, trifluoperazine microencapsulated (dose 10 mg/kg) and dispersed in sesame oil for injection.*

Table II—Drug Solubilities at 37° in pH 7.4 Buffer

Drug	Solubility, 10^6 M
Trifluoperazine	36
Trifluoperazine embonate	30
Pericyazine	104
Pericyazine embonate	63
Fluphenazine	71
Fluphenazine embonate	25
Fluphenazine enanthate[a]	0.2

[a] The solubility of fluphenazine enanthate was determined in various aqueous ethanol solutions, and the logarithm of solubility was plotted against percent ethanol (six points). Extrapolation to zero ethanol gave the value quoted in the table.

These results are summarized in Table I.

DISCUSSION

The approach made here to prolong drug activity is typical of previous attempts in this field (3). Wai *et al.* (8), formulating a long-acting pentagastrin preparation, increased vehicle viscosity, formed a suspension, and finally coated the suspended particles to give the desired extension of drug activity. Formation of drug–embonate complexes was used successfully to prolong the release of intramuscular dihydrostreptomycin (9) and cycloguanil (10) but had little value in usefully extending the duration of activity of the three studied phenothiazines.

The lack of difference in activity between the trifluoperazine hydrochloride in aqueous solution and the embonate in suspension and solution may be due to the similarity in solubilities of these salts in pH 7.4 buffer, which has a pH close to that of the tissue fluids. Trifluoperazine hydrochloride has a solubility of 36×10^{-6} M at 37°, while the embonate has a solubility of 30×10^{-6} M at 37° (Table II). Thus, trifluoperazine precipitates from either hydrochloride or embonate solutions on encountering a pH of 7.4 at the injection site. Pericyazine is more soluble and appears to have a shorter duration of activity in all forms. The fluphenazine enanthate has a very low solubility (2×10^{-7} M), which undoubtedly contributes to its prolonged action.

Multiple emulsions of antitoxins extended antibody response time after injection (11), and this technique was used to give slow release of chemotherapeutic agents (12, 13). Our multiple emulsion formulation showed promise but had insufficient stability to prolong complete activity beyond 3 days. Undoubtedly, a stable emulsion system would be of interest. The logical extension of these approaches was to use microencapsulated drug derivatives; in this instance, the formulation performance approached the desired objective.

The microencapsulating agent used (nylon 610) was chosen to determine the feasibility and suitability of the microencapsulation technique for long-acting parenterals. Nylon is not likely to be acceptable in human medicine. Control of drug release by increasing the amount of nylon-forming materials, or alternative polymers (piperazine–phthalamide) or gelatin produced by coacervation, has been attempted. No significant improvement over the best results shown in this paper has been achieved.

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