Some Studies of a Sustained Release Principle

By C. J CAVALLITO, LESTER CHAFETZ, and LOWELL D. MILLER

Urinary excretion of drug after oral dosage of chlorpheniramine as maleate salt and in an oral sustained release formulation was studied, and the urinary excretion and plasma levels of tritium radioactivity obtained after crossover administration of tritium-tagged phenylephrine as hydrochloride and in sustained release formulation were compared. The urinary excretion of both drugs varied widely among individuals, indicating that this parameter is limited in value as a reflection of oral absorption. No relation between blood level and excretion of tritiated phenylephrine was apparent.

THE DEVELOPMENT of oral sustained release forms of medication, which was receiving but scant attention about ten years ago, became a subject of increasing interest following successful introduction of the early products in this field. The increased awareness of the potentials of oral sustained release products has not only led to the development of additional techniques for providing the desired effects, but has also attracted the attention of academic investigators as well as of regulatory agencies. Lazarus and Cooper (1) have provided timely reviews of the subject.

A sustained release product should provide improved performance of a drug as well as the added convenience of fewer doses. Such a product should prevent too rapid a release rate of an absorbable form of drug and permit its gradual availability for absorption over a prolonged period of time. Ideally, these rates of absorption should be tailored as closely as possible to meet the drug requirements of the body without eliciting undesirable effects. There are drugs which obviously have no need for or do not benefit from sustained release formulations.

The interest in our laboratories in oral sustained release products evolved from some simple studies about ten years ago which showed that *Veratrum* alkaloids were relatively well-tolerated orally when utilized as the tannate salt complexes. Investigations showed that a variety of drugs which are organic amines can be converted to stoichiometrically homogeneous pentaamine gallotannates, which are stable, tasteless substances of limited aqueous solubility and which, in the presence of aqueous solutions of electrolytes, provide a gradual release of soluble therapeutic amine salt (2). Since the goal was to provide drug which would be available over a prolonged period of time without initial overdosage, and since stomach acid could lead to too rapid a release of amine from its tannate, it was determined that intimate combination with a polymeric, polyanionic agent, such as polygalacturonic acid, could protect the tannate from too rapid solution in acids. Using as a guide the responses in humans administered a variety of dosage preparations, there was developed an oral sustained release principle which utilizes amine tannates and polygalacturonic acid in such proportions that rate of release and absorption of the amine drug can occur gradually over a wide range of pH values.[1] The polygalacturonic acid, which prevents too rapid a solubilization of amine from the tannate in the acid media, itself becomes more soluble as the gut becomes less acid. Ultimately, all components may become individually dissolved. Since the specially prepared solid and liquid dosage forms disperse to a colloidal state in aqueous media, they should tend to empty from the stomach gradually and continue to be available at intestinal sites of absorption over an extended period of time. [Wagner (3) has critically reviewed the effect of particle number and size as related to gastric emptying and the onset of therapeutic effect of sustained release drugs.]

A variety of therapeutic and chemical categories of amine drugs have been converted to this type of sustained release product and evaluated largely on the basis of their clinical performance relative to that of the usual, nonsustained release forms of the drugs (4–16). Following demonstrated performance in man, ancillary studies were carried out with these preparations in an attempt to obtain more quantitative measures of drug action. Some of these *in vivo* studies are reported and their uses and limitations discussed.

EXPERIMENTAL

Urinary Excretion of Chlorpheniramine.—Urinary excretion of chlorpheniramine was measured after the administration of the drug in nonsustained re-

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[1] This type of sustained release product is referred to by the trade name of Durabond by Irwin, Neisler & Co.

lease and in sustained release forms. The sustained release form utilized the tannate salt[2] of chlorpheniramine, and chlorpheniramine maleate served as the more rapidly absorbable form of the drug. Each subject was given, at weekly intervals, unit doses of 10.2 mg. of chlorpheniramine maleate (7.17 mg. base) in small gelatin capsules and 30 mg. of chlorpheniramine tannate (13.4 mg. base). Following ingestion of drug, urine samples were voided at specified intervals corresponding to times at which urine blanks were obtained on each subject. Urine samples were made alkaline with sodium hydroxide, and the drug was extracted into chloroform. The chloroform was washed with pH 10 borate buffer to reduce the blank readings, then extracted with dilute aqueous acid. The concentration of chlorpheniramine was estimated from the absorbance of the acid solution at 265 mμ determined with a Beckman model DU spectrophotometer. The isolation procedure gave satisfactory recoveries (98.4%) of chlorpheniramine four hours after its addition to urine.

Plasma Levels and Urinary Excretion Rate of Tritium-Labeled Phenylephrine.—Several years ago, a study in humans was initiated for the purpose of determining the rates of appearance of a radioactive drug component in blood following its oral administration in conventional and in Durabond-type preparations. Phenylephrine with random tritium tagging was used as the test drug. The investigation was conducted in cooperation with the Nuclear Science and Engineering Corporation, and the technique used in the pilot study was described by Bogner and Walsh (17). A more extensive study was completed more recently in which both blood levels and urinary excretion of drug were measured.

Twelve adult male subjects with no known disorders of absorption or excretion were used in the study. They were given doses of tritiated phenylephrine as hydrochloride and as tannate in similar appearing tablets at intervals of a week. Six subjects (age range: 23–39 years; weight range: 150–206 lbs.) were given doses of phenylephrine tannate equivalent to 15.68 mg. base, and phenylephrine hydrochloride corresponding to 7.4 mg. base was selected for comparison. These were doses which in practice provided comparable initial therapeutic responses and which in earlier pilot studies yielded initially comparable drug blood levels.[3] In another six subjects administered half these doses, the lower radioactivity levels showed relatively large standard deviations and were of questionable quantitative significance. Even with the higher doses, the standard deviations were appreciable.

All doses were given after an overnight fast, and the subject was allowed four ounces of water immediately after taking each tablet. Identical light meals were ingested by each subject 1 hour after dose administration. Blood samples (15 ml.) were obtained at indicated intervals from the antecubital veins. Plasma was immediately separated by centrifugation and frozen until analyzed. Total urine collections were made as voided at five interval periods up to 48 hours. Details of the analytical procedures used for determination of tritium radioactivity in plasma and urine samples are described elsewhere (17).

RESULTS AND DISCUSSION

Chlorpheniramine Urinary Excretion.—The quantities of chlorpheniramine found in the urine of four subjects after oral dosage of chlorpheniramine maleate and of three of the same four (one subject became unavailable) after oral dosage of the drug in the tannate form are shown in Table I.

Table I.—Interval Excretions of Chlorpheniramine[a] in Urine After Oral Dose

Hours	Subject I	Subject II	Subject III	Subject IV
	Chlorpheniramine Maleate[b]			
2	0.00	0.15	0.02	0.05
4	0.39	0.28	0.07	0.00
6	0.84	0.52	0.12	0.10
8	0.64	0.44	0.07	0.05
10	0.62	0.40	0.07	0.06
12	0.60	0.25	0.06	0.28
15	0.30	0.25	...	0.07
24	0.70	0.54	0.43	0.29
28	0.90	0.20	...	...
34	1.00	0.06	...	...
	Chlorpheniramine Tannate[c]			
3	0.56	0.30	0.00	...
6	0.41	0.76	0.40	...
9	0.19	0.33	0.59	...
12	0.66	0.72	0.46	...
24	1.79	1.43	0.90	...
29	0.77	...	...	...
32	...	0.48	0.63	...

[a] As mg. base. [b] 7.17 mg. base. [c] 13.4 mg. base.

The doses of each form selected were those which represented equivalents in terms of initially induced therapeutic response. The data for the rapidly absorbable form show a considerable difference and irregularity among subjects in their period of maximum excretion and in the total amount of drug excreted. These differences appear to be less after dosage of the sustained release form of the drug.

Variations in Urinary Excretions.—The wide variation among individual excretions of chlorpheniramine with these few subjects raised questions as to the significance of such measurements as reflections of rate of absorption of this antihistaminic and possibly of other drugs. A review of the published literature purporting to relate urinary excretion to drug absorption rates showed that wide individual variations also were evident from the data of others but that usually little if any note was made of this in plotting cumulative averaged values. Following oral administration of a drug, wide variations are evident among individual excretions, particularly during the first few hours, and as cumulative values are shown with time, the interval excretion variations tend to cancel one another to provide more uniform total recoveries. Wide variations in excretion (of drug or metabolite) following oral administration of single doses of

[2] Reference to tannates throughout this report denotes their incorporation with polygalacturonic acid in Durabond formulations.

[3] From a practical use basis, we were interested in the relative duration of action of dosage forms producing an adequate therapeutic response without undesirable side reactions.

drugs, particularly during the earlier intervals, may be illustrated by published data (Table IV) (18–26). All of these reports (except reference 26) measured only urinary excretion of drug or metabolites and not drug blood concentrations. A more comprehensive study utilizing sulfaethylthiadiazole was reported by Swintosky, *et al.* (26–28), in which both blood and urine drug levels were measured. This drug, which is virtually all excreted in 72 hours, also showed considerable individual variations in excretion levels in the first 3-hour period even with parenteral administration of the drug and these variations tended to decrease with increase in administered dosage.

Phenylephrine Plasma Levels and Urinary Excretion Rates.—The tritiation tagging technique was used to measure blood concentrations and urinary excretions of drug following administration of soluble and tannate forms of phenylephrine in that there was not available a sufficiently sensitive chemical method at the time of the study. [Since the completion of this study a fluorometric method for the determination of phenylephrine in blood has been reported (29).] Although there is no absolute evidence that the tritium level represents unchanged phenylephrine, nevertheless the measure of tritium radioactivity does directly reflect phenylephrine which has been absorbed and does permit comparison of the dosage forms. The tritium-labeled phenylephrine had been recrystallized under conditions which removed labile tritium (17) and minimized the possible influence of tritium exchange during the experimental period. The tritium activity values, expressed in terms of micrograms of phenylephrine base per 100 ml. of plasma, are given in Table II for phenylephrine hydrochloride and for the tannate. The mean values are graphically represented in Fig. 1. Trit-

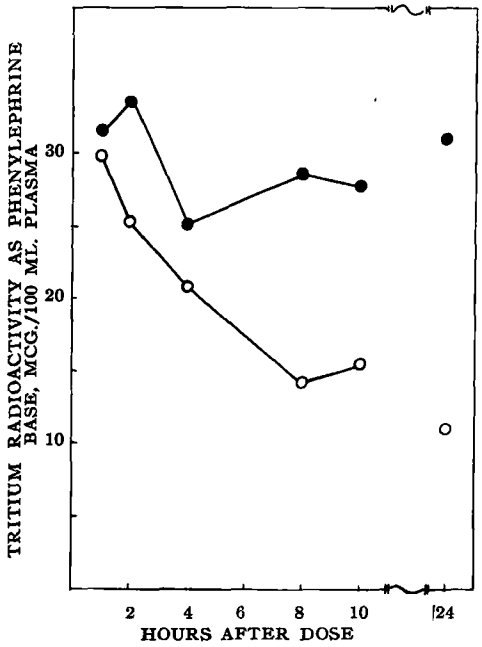

Fig. 1.—Mean plasma levels of tritium radioactivity expressed as phenylephrine base after oral dose of 7.38 mg. base as hydrochloride, O, and 15.68 mg. base as tannate, ●.

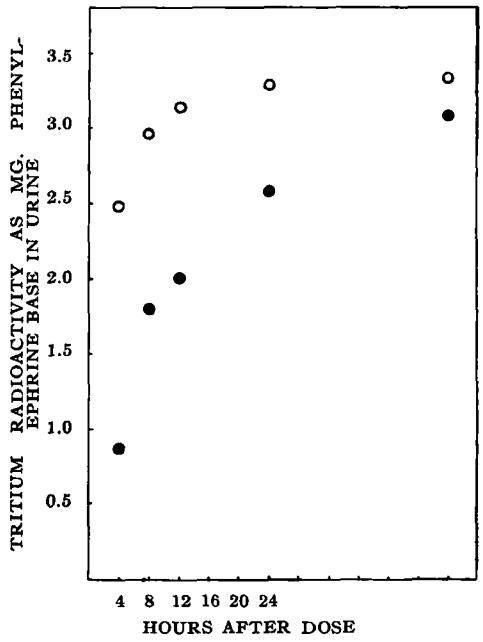

Fig. 2.—Cumulative mean tritium radioactivity expressed as phenylephrine base after oral dose of 7.38 mg. base as hydrochloride, O, and 15.68 mg. as tannate, ●.

TABLE II.—TRITIUM ACTIVITY IN PLASMA AFTER DOSE OF TAGGED PHENYLEPHRINE[a]

Hours	Subject I	II	III	IV	V	VI	Mean ± S.D.
			Phenylephrine Hydrochloride[b]				
1	36.4	47.3	29.2	24.1	16.8	25.5	29.8 ± 10.7
2	31.3	29.9	31.3	19.0	23.3	16.8	25.3 ± 6.5
4	26.2	17.5	30.6	16.8	17.5	16.8	20.8 ± 6.0
8	7.3	18.2	16.8	10.2	17.5	15.3	14.2 ± 4.5
10	10.9	18.2	29.9	14.5	9.4	10.2	15.5 ± 7.7
24	18.2	5.8	13.9	5.8	10.9	11.7	11.0 ± 4.8
			Phenylephrine Tannate[c]				
1	29.9	29.9	34.3	39.8	36.2	39.8	31.6 ± 9.4
2	36.2	34.3	37.9	25.2	18.0	50.5	33.6 ± 11.6
4	10.8	25.2	32.6	23.5	32.6	27.1	25.2 ± 8.0
8	23.5	30.8	32.6	18.0	43.4	23.5	28.6 ± 8.9
10	25.2	23.5	39.8	25.2	19.9	32.6	27.8 ± 7.2
24	34.3	45.1	23.5	25.2	25.2	32.6	31.0 ± 8.1

[a] Expressed as mcg./100 ml. plasma. [b] 7.38 mg. base. [c] 15.68 mg. base.

ium levels expressed as phenylephrine base recovered in urine during intervals following ingestion of the hydrochloride and tannate forms are presented in Table III for these subjects, and the mean cumulative amount of radioactivity expressed as phenylephrine base is plotted for both dosage forms in Fig. 2. The plotting of mean cumulative values is a rather conventional procedure but, as noted earlier, this can leave a misleading impression of uniformity or consistency of excretion patterns.

Fairly similar mean tritium blood levels are provided (Fig. 1) at the first hour by the doses utilized of rapidly soluble and sustained release forms of phenylephrine. The blood levels are definitely maintained closer to this initial value for a considerably greater time from the sustained release than from the rapidly soluble drug form. Drug blood concentrations may not necessarily be directly related to therapeutic responses but the results are at least consistent with the clinical reports on the sustained effects of the principle.

If one compares tritium interval excretion with average blood levels during that interval (the shorter the interval the more valid the comparison, however, physical limitations should be recognized), there is observed a rather poor correlation. Particularly puzzling is the much greater difference in urinary excretion than in the blood levels from the two drug forms in the first 4 hours. Thus, although the two drug forms show no great dif-

TABLE III.—TRITIUM RADIOACTIVITY IN URINE AFTER DOSAGE OF TAGGED PHENYLEPHRINE[a]

Hours	Subject I	II	III	IV	V	VI	Mean ± S.D.
				Phenylephrine Hydrochloride[b]			
0–4	3.66	3.02	1.42	2.36	3.36	1.08	2.48 ± 1.05
4–8	0.40	0.23	0.17	0.24	0.75	1.07	0.48 ± 0.36
8–12	0.10	0.07	0.19	0.21	0.15	0.30	0.17 ± 0.08
12–24	0.21	0.31	0.44	0.28	0.44	0.39	0.35 ± 0.09
24–48	0.11	0.09	0.12	0.12	0.22	0.24	0.15 ± 0.14
				Phenylephrine Tannate[c]			
0–4	2.46	0.74	0.78	0.29	0.25	0.71	0.87 ± 0.81
4–8	0.24	0.92	0.85	0.58	1.85	1.08	0.92 ± 0.54
8–12	0.16	0.17	0.13	0.28	0.28	0.22	0.21 ± 0.06
12–24	0.26	0.89	0.46	0.35	0.91	0.59	0.58 ± 0.27
24–48	0.20	0.70	0.60	0.50	0.38	0.61	0.50 ± 0.18

[a] Expressed as mg. phenylephrine. [b] 7.38 mg. base. [c] 15.68 mg. base.

TABLE IV.—SOME REPORTED RANGES IN DRUG EXCRETIONS WITH EMPHASIS ON EARLY INTERVALS

Reference	Drug	Oral Dose, mg.	Number Subjects	Period, hr.	Excretion Range Min.	Max.
18	Aspirin B	600	14	1	6.1	34.0
18	Aspirin D	600	14	1	1.5	28.3
18	Aspirin E	600	14	1	4.2	17.1
18	Aspirin B	600	14	9	121	388
18	Aspirin D	600	14	9	146	362
18	Aspirin E	600	14	9	178	335
19	Aspirin	1000	9	1	7.3	28.2
19	Al aspirin	1120	9	1	3.6	8.4
19	Aspirin	1000	5	1	18.9	39.5
19	Aspirin	500	5	1	8.24	20.6
19	Al aspirin	1120	5	1	1.34	13.6
20	Aspirin	650	5	1	20.6	45.6
20	Aspirin	650	5	4	189.0	251.2
20	Benzylpenicillin	100,000[a]	5	0.5	0	3100[a]
20	Benzylpenicillin	100,000[a]	5	5	10,200[a]	26,300[a]
20	Sulfaethylthiadiazole	1000	7	0.5	0	42.5
20	Sulfaethylthiadiazole	1000	7	8	305.7	589.1
21	Phenylpropanolamine hydrochloride	50	3	2	7.4	16.6
21	Phenylpropanolamine hydrochloride	50	3	24	45.2	50.5
22	Tolbutamide	250	4	1	1	11
22	Tolbutamide	250	4	3	4	19
22	Tolbutamide (Na)	250	4	1	9	28
22	Tolbutamide (Na)	250	4	3	81	123
23	Na paraaminosalicylate (solution)	500	7	2	161	306
23	Na paraaminosalicylate (solution)	500	7	4	261	375
24	Tetracycline hydrochloride	200	6	1	1.8	5.5
24	Tetracycline hydrochloride	200	6	2	6.5	20.8
24	Tetracycline hydrochloride	200	6	4	17.5	36.0
24	Tetracycline·mucic acid	200	6	1	0	2.7
24	Tetracycline·mucic acid	200	6	4	2.2	23.0
25	Nicotinic alcohol ("Timespan")	300	3	4	3	3.6
25	Nicotinic alcohol ("Timespan")	300	3	24	27	34.2
26	Sulfaethylthiadiazole	500[b]	4	3	29	113
26	Sulfaethylthiadiazole	1000[b]	4	3	204	296

[a] Units. [b] Intravenous.

ference in mean blood levels during the first 4 hours, the mean urinary excretion values are in the ratio of 2.48 to 0.87 (hydrochloride to tannate) for this interval. From 4–48 hours the mean urinary excretion ratio was 1.15 to 2.21 (hydrochloride to tannate) and this more closely reflected the blood level patterns.

The question arose as to whether a peak blood level might have been provided by the rapidly soluble drug form in less than 1 hour and that this led to the large excretion. To determine this, several of the same subjects were again given the hydrochloride form of the drug about 3 months later, and blood levels were measured after one-half hour as well as 1 hour. In four of five repeated subjects the blood levels were considerably lower in the half-hour reading than after 1 hour; in subject III blood levels were negligible at both periods; whereas in the previous test the same subject gave a 1-hour level near the mean for the group. The higher urinary excretion in the comparative study would thus be difficult to explain on a basis of very high blood levels within a half hour or less after drug administration.

The new data reported here and most of that previously published by others show that urinary excretion of drugs and their metabolites varies very widely among individuals, particularly with lower dosage of drugs and during the first few hours after administration. In those few instances in which both drug blood concentrations and urinary excretions are measured, there is found to be rather inconsistent correlation among individuals. The use of drug excretion rate measurements as reflections of oral absorption from sustained release formulations is of questionable value.

SUMMARY AND CONCLUSIONS

With the drugs, chlorpheniramine and phenylephrine, urinary excretion in man shows wide individual variations and is indicated to be an unreliable reflection of rate of oral absorption. This also is evident from published data with other drugs, particularly as pertains to the first few hours after drug administration. Plotting of cumulative excretion values tends to obscure interval variations.

Rapidly absorbable and sustained release formulations containing tritiated phenylephrine were administered in doses which provided similar early blood levels. There is little relation between urinary excretion and blood concentrations of tritiated drug during the first few hours. The sustained release form maintained blood levels at near the first hour's value for a considerably longer period of time than did the rapidly soluble drug form.

More information is needed with regard to interrelationships of absorption, blood concentrations, and urinary excretion of rapidly soluble forms of drugs before one can assume that urinary excretion profiles are true reflections of rates of absorption of drugs from oral sustained release preparations. The wide variations among these parameters in the first few hours after drug administration particularly merits more attention.

REFERENCES

(1) Lazarus, J., and Cooper, J., *J. Pharm. Pharmacol.*, **11**, 257(1959); THIS JOURNAL, **50**, 715(1961).
(2) Cavallito, C. J., and Jewell, R., *ibid.*, **47**, 165(1958).
(3) Wagner, J. G., *ibid.*, **50**, 359(1961).
(4) Garrett, T. A., *Clin. Med.*, **3**, 1185(1956).
(5) Bensoussan, P., *Ars Medici*, **12**, 159(1957).
(6) Kile, R. L., *Antibiot. Med. Clin. Therapy*, **5**, 578 (1958).
(7) Lawler, E. G., and Limperis, N. M., *Clin. Med.*, **5**, 1669(1958).
(8) Kroger, W. S., *Am. Pract.*, **10**, 2169(1959); *Intern. Rec. Med.*, **172**, 212(1959).
(9) Steller, R. E., DeMar, E. A., and Schwartz, F. R., *Ind. Med. Surg.*, **28**, 362(1959).
(10) Villanyi, L., and Stillwater, R. B., *Eye, Ear, Nose, Throat Monthly*, **38**, 650(1959).
(11) Fontana, V. J., *Ann. Allergy*, **18**, 1107(1960).
(12) Lanoff, G., *Illinois Med. J.*, **117**, 16(1960).
(13) Sherwood, H., and Epstein, J. I., *N. Y. State J. Med.*, **60**, 1793(1960).
(14) Simon, D. L., *Clin. Med.*, **7**, 1761(1960).
(15) Thomley, M. W., Orr, L. M., Campbell, J. L., and Jamison, J. B., *J. Am. Med. Assoc.*, **172**, 1634(1960).
(16) Robin, B. A., *Med. Ann. Dist. Columbia*, **9**, 525 (1961).
(17) Bogner, R., and Walsh, J., THIS JOURNAL, in press.
(18) Levy, G., *ibid.*, **50**, 388(1961).
(19) Levy, G., and Sahli, B. A., *ibid.*, **51**, 58(1962).
(20) Nelson, E., and Schaldemose, I., *ibid.*, **48**, 489(1959).
(21) Heimlich, K. R., MacDonell, D. R., Flanagan, T. L., and O'Brien, P. D., *ibid.*, **50**, 232(1961).
(22) Nelson, E., Knoechel, E. L., Hamlin, W. E., and Wagner, J. G., *ibid.*, **51**, 509(1962).
(23) Chapman, D. G., Crisafio, R., and Campbell, J. A., *ibid.*, **45**, 374(1956).
(24) Nelson, E., *ibid.*, **48**, 96(1959); **49**, 54, 437(1960).
(25) DeRitter, E., *Drug Std.*, **28**, 33(1960).
(26) Swintosky, J. V., Robinson, M. J., and Foltz, E. L., THIS JOURNAL **46**, 403(1957).
(27) Swintosky, J. V., Foltz, E. L., Bondi, A., Jr., and Robinson, M. J., *ibid.*, **47**, 136(1958).
(28) Swintosky, J. V., Bondi, A., Jr., and Robinson, M. J., *ibid.*, **47**, 753(1958).
(29) Rubin, M., and Knott, L. B., *Clin. Chem.*, **1**, 573 (1961).